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Drinking Water Criteria Document for Fluoride

Life Systems, Inc., Cleveland, OH

Prepared for

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CRITERIA DOCUMENT ON FLUORIDE

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for

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on Fluoride. This document was previously published in a draft form (PB 85 199 321) and has been revised. This Criteria Document is an extensive review of the following topics:

-Physical and chemical properties of fluoride.
-Toxicokinetics and human exposure to fluoride.
-Health Effects of fluoride in humans and animals.
-Mechanisms of toxicity of fluoride.
-Quantification of toxicological effects of fluoride.

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I. INTRODUCTION

The fluoride ion (F^-) is ubiquitous and occurs in igneous and sedimentary rock, soil, surface water, sea water and air. Elemental fluorine (F_2) is a pale yellow, acrid gas at 20°C, with a freezing point of -219.6°C and a boiling point of -188.2°C. Fluorine is highly reactive; however, the fluoride ion occurs naturally in combined, mineral forms such as fluorspar, fluorapatite and cryolite as well as in aluminum, calcium and magnesium salts. Industrially, fluorspar is treated with sulfuric acid to produce hydrofluoric acid (HF), the intermediate from which other fluorine compounds, such as sodium fluoride (NaF), are prepared. Sodium fluoride is used commercially in fluxes, for drinking water fluoridation, in tablets and topically applied preparations for the prevention of dental caries and for scrubbing HF from fluorine. Sodium fluoride is occasionally used as an insecticide and as a wood preservative.

Approximately 97% of ingested fluoride is rapidly absorbed from the gastrointestinal tract of the rat and the human. The absorbed fluoride is distributed throughout intracellular and intercellular spaces by the blood. Although appreciable quantities of fluoride are not stored in soft tissue, its rapid uptake and bioconcentration in bone and teeth are functions of both concentration and duration of exposure. Concentrations in bone increase with increasing age. Absorbed fluoride is usually excreted in urine or deposited as fluorapatite in calcified tissues. Under steady-state intake conditions, the urinary concentration of fluoride in adults tends to approximate the fluoride concentration of the drinking water. Fluoride may be excreted through perspiration in hot environments.

Drinking water, food and air are the main sources of fluoride exposure for humans. In general, a 70-kg adult male takes in up to 1.2 μg F/day in air, 0.2 to 0.8 mg F/day in food and 0.2 to 2.0 mg F/day in water. On a per body weight basis these values are 1.7×10^{-5} mg/kg/day for air, 2.9×10^{-3} to 1.1×10^{-2} mg/kg/day for food and 2.9×10^{-3} to 2.9×10^{-4} mg/kg/day for water. Thus, compared to food and water, the contribution of fluoride by air is negligible. Under typical exposure conditions (1.0 mg F/L), adult males consume 72% to 91% of their fluoride intake via drinking water; for five- to thirteen-year-old children the range of fluoride intake via drinking water is 64% to 97%. (At exposures greater than 2.0 mg F/L, drinking water accounts for over 90% of the exposure for both groups). On a per body weight basis, five- to thirteen-year-old children consume 1.4 times as much fluoride via drinking water as adult males, and newborn, formula-fed infants consume more than eight times as much as adults.

Acute lethality of NaF in animals varies with route of administration, age and sex. In mice the oral LD_{50} was 46.1 mg F/kg compared to an intravenous LD_{50} of 23.0 mg F/kg. The approximate intraperitoneal LD_{50} of NaF in adult rats is 26 mg F/kg. Young rats (less than seven months of age) and specifically young male rats appear to be resistant to NaF toxicity. Acutely toxic doses of fluoride in rats occasionally resulted in fatal polyuria, but 100 mg F/L in drinking water did not cause renal injury.

Cattle tolerated 27 ppm (equivalent to 0.64 mg F/kg/day) in the diet without observable deleterious effect. Cattle chronically exposed to 49 ppm fluoride in the ration (equivalent to 1.17 mg F/kg/day) showed skeletal and dental fluorosis. Sheep were less sensitive than cattle to the chronic effects of fluoride. Growth in most species was unaffected by dietary concentrations of 100 ppm or less; however, growth in cattle appeared to be slightly affected at 40 ppm. Cardiovascular effects were observed in dogs at 9 mg F/kg or higher. At concentrations of 50 mg/L or below of fluoride in drinking water, no structural or functional changes in the thyroid have been observed in animals. No conclusive evidence has been found to indicate that fluoride is mutagenic or carcinogenic either in vitro or in vivo.

The beneficial effects of fluoride on human health have been demonstrated, both in terms of general health and in the treatment of specific diseases. Fluoride ingested during childhood results in a marked reduction of dental caries. Similarly, fluoride has found application in stimulating substituted bone growth in patients with osteoporosis. The daily intake levels considered to be protective against both dental caries and possibly osteoporosis are established by age category with 1.5 to 4.0 mg/day (0.7 to 2.0 mg/L in drinking water) the range for adults. Fluoride has also been suggested to have beneficial effects on the cardiovascular system (reduced aortic calcification) and hearing (stabilization of patients with active otospongiosis).

Incidences of human poisoning from NaF have been reported. The estimated lethal dose for humans is 70 to 140 mg/kg. Hypothetical relationships between mongolism and sensitivity to fluoride, as well as exposure to fluoride and cancer incidence have been reported but not substantiated. Persons with renal insufficiency may be at increased risk to the toxic effects of fluoride.

Delayed skeletal maturation has been reported in children exposed to water containing as little as 3.6 mg F/L. These data, however, were derived from a study of 11- to 15-year-old Tanzanian girls and several confounding factors (i.e., warm climate, drinking water intake, nutritional status, incidence of other diseases, etc.) prevent drawing any conclusions from this study for application to the U.S. situation. Skeletal fluorosis (as measured by increased bone density) has been observed in populations using drinking water containing from 4 to 8 mg F/L. Severe skeletal fluorosis has occurred in both adults and children who consumed drinking water containing 10 or more mg F/L.

Dental fluorosis occurs during the developmental period of enamel formation. Epidemiological studies have shown that dental fluorosis is a function of fluoride concentration, age, duration of exposure and possibly ambient temperature (as related to water consumption). In nearly all epidemiological evaluations, including warm climates, objectionable (moderate and severe) dental fluorosis is generally not observed in a significant percentage of the population at drinking water concentrations below 2.0 mg F/L. There is no evidence of adverse health effects in humans resulting from properly controlled fluoridation of domestic water supplies.

Fluoride interacts with bones and teeth by replacing hydroxyl or bicarbonate radicals in hydroxyapatite to form fluorohydroxyapatite. The presence of fluorohydroxyapatite increases the crystalline structure of the bone and reduces its solubility. This is believed to increase the resistance of teeth to dental caries and, possibly, to decrease the incidence of osteoporosis. As bone crystal growth continues, fluoride is incorporated into the inner layers of the crystals as well as on the surface. The available evidence suggests that dental fluorosis results from the effects of fluoride on the epithelial enamel organ. Specifically, several studies have shown that ameloblasts are susceptible to fluoride. Dental staining often accompanies fluorosis but does not determine the degree of the fluorosis.

Populations that appear to be at increased risk from the effects of fluoride are individuals that suffer from diabetes insipidus or some forms of renal impairment. These high risk populations represent a relatively small segment of the general population.

There is a general absence of suitable experimental or clinical data following short-term oral exposure to fluoride for the derivation of one-day or ten-day Health Advisory values for children and adults. The dose-response for dental fluorosis, while subject to considerable variation at different locations and in different populations, represents a steady increase in moderate and severe dental fluorosis with increasing fluoride concentration in the drinking water. It is generally observed that the incidence of moderate and severe dental fluorosis begins to impact a marked segment of the population when the drinking water concentration approaches and exceeds 2.0 mg F/L. One recent study of children suggested that the maximum protection from dental caries was achieved when drinking water contained approximately 2 mg F/L.

Various studies and reviews indicate that the no-effect levels for the initial signs of skeletal fluorosis (increased bone density) in adults appear to be at drinking water concentrations between 3.0 and 8.0 mg F/L. Protection of human health from this effect is believed to be achieved at 4.0 mg F/L with an adequate margin of safety. There is no valid evidence to classify fluoride as a potential carcinogen.

The National Academy of Sciences has estimated an adequate and safe total intake of fluoride ranging from 0.1 to 0.5 mg/day for infants (less than six months old) to 1.5 to 4.0 mg/day for adults. These estimates are considered protective against dental caries and possibly osteoporosis.

II. PHYSICAL AND CHEMICAL PROPERTIES

A. Physical and Chemical Properties

Elemental fluorine is highly reactive. Fluorine is a pale yellow, acrid gas with a freezing point of -219.6°C and a boiling point of -188.2°C (Weast 1980). However, fluorine is widely disseminated in ionic or combined forms. The terms "fluorine" and "fluoride" are both used in the general literature to refer to combined forms of fluorine.

The fluoride-containing minerals fluorspar, fluorapatite and cryolite are essentially insoluble in water. They have very high melting and boiling points and very low vapor pressures (Drury et al. 1980).

There are hundreds of ionic compounds of fluorine. Some commercially important ionic fluorides are the sodium, calcium, aluminum and magnesium salts; these have characteristically high melting and boiling points. Sodium fluoride is a white crystalline powder with a melting point of 993°C and a boiling point of 1695°C. This compound is only minimally soluble in water (4.22 g/100 mL at 18°C) (Weast 1980). Aluminum, calcium and magnesium fluorides are also only sparingly soluble in water.

Hydrogen fluoride is a colorless liquid or gas with a boiling point of 19.5°C and a freezing point near -83°C (Weast 1980). Hydrogen fluoride is highly soluble in water and fumes strongly in contact with the atmosphere.

Hydrogen fluoride has a high vapor pressure (17.8 psia at 25°C) and its liquid density is 0.9576 g/cm^3 at 25°C (Gall 1966).

Silicon tetrafluoride is a colorless gas with a melting point of -90°C, a boiling point of -86°C (Weast 1980) and an odor reminiscent of hydrogen chloride (Windholz et al. 1976). It reacts with water to form fluorosilicic acid (H_2SiF_6), which is very soluble in water.

Fluorine also combines covalently with organic compounds. There are thousands of known fluorine-containing organic compounds, but few of these occur naturally. The chemical and physical properties of many of these compounds differ greatly from their hydrocarbon counterparts, mainly because of the stronger carbon-fluorine bond (Drury et al. 1980).

Table II-1 summarizes the properties of most of the naturally occurring fluorine compounds and various fluorine compounds used industrially.

B. Manufacture and Uses

Of the three major fluoride-containing ores (fluorspar, phosphate rock and fluorapatite), only fluorspar is used commercially as a source of fluorides. Generally, fluorspar is treated with sulfuric acid to produce hydrogen fluoride. Hydrogen fluoride is the most important manufactured fluoride and is the intermediate from which other fluorine compounds are prepared. About 292,000 metric tons of HF were produced in the United States in 1977 (Drury et al. 1980). Approximately 40% was used to manufacture aluminum, 37% was converted

Table II-1 Selected Fluoride Compounds and Properties

Substance	Formula	Color	Melting Point (°C)	Boiling Point (°C)	Density (g/cm^3)[a]	Solubility in Water (g/100 ml)	Vapor Pressure (mm Hg)
Fluorine	F_2	yellow	-219.62	-188.14	1.90 (solid)	react	760 (-187.9)
Mineral Fluorides							
Fluorspar	CaF_2	white	1402	2513	3.18 (solid)	0.0016 (18°C)	7.6 (2100°C)
Cryolite	$3NaF\ AlF_3$	white	1009	---	2.97 (solid)	0.042 (25°C)	1.9 (1009°C)
Fluorapatite	$3Ca(PO_4)_2 \cdot CaF_2$	---	1630	---	3.18 (solid)	insoluble	---
Ionic Fluorides							
Aluminum Fluoride	AlF_3	white	1040	1291	3.07	0.559 (25°C)	760 (1537)
Calcium Fluoride	CaF_2	white	1402	2513	3.18	0.0016 (18°C)	7.6 (2100°C)
Magnesium Fluoride	MgF_2	white	1225	2260	3.0	0.0076 (18°C)	---
Sodium Fluoride	NaF	white	993	1695	2.558	4.22 (18°C)	---
Covalent Fluorides							
Hydrogen Fluoride	HF	colorless	-83.7	19.5	1.0015 (0°C)	miscible	760 (19.7)
Silicon Tetrafluoride	SiF_4	colorless	-90	-86	1.66 (-95°C)	reacts	760 (-94.8)
Fluorosilicic Acid	H_2SiF_6	---	---	108.5 (30% soln)	1.274 (25°C) (30% soln)	very soluble	7201 (25°C) (30% soln)
Organic Fluorides							
Trichlorofluoromethane	CCl_3F	---	-111	23.8	1.467	0.011 wt% (25°C)	760 (23.7)
Dichlorodifluoromethane	CCl_2F_2	---	-158	-29.8	1.311	5.7 (26°C)	760 (-29.8)
Tetrafluoromethane	CF_4	---	-184	-128.0	1.317 (-80°C)	0.0015 wt% (25°C)	760 (-127.7)
Fluoromethane	CH_3F	---	-142	-78.4	1.587 (-73°C)	---	760 (78.2)
Fluoroethane	C_2H_5F	---	-143	-37.1	1.519 (-76°C)	---	760 (-32.0)
Fluoroethene (vinyl fluoride)	C_2H_3F	---	-160	-72.0	0.675 (10°C)	0.94 (80°C, 500 psia)	760 (-72.2)
Tetrafluoroethylene	C_2F_4	---	-142.5	-76.3	1.519 (-76°C)	---	216.2 psia (0°C)
Hexafluoropropene	C_3F_6	---	-156.2	-29.4	1.583 (-40°C)	---	---

[a] Density given at 25°C unless noted otherwise.

Adapted from Drury et al. 1980 (based on Horton 1961; Windholz et al. 1976; Byrne 1966; Weast 1978; Gall 1966); Weast 1980 and Perry and Chilton 1973.

into fluorocarbon compounds, 7% was used in processing uranium, 5% was used in alkylation catalysts in petroleum refining, 4% was used in manufacture of fluoride salts and 4% was used in stainless steel pickling operations. Smaller quantities were used as fluxes in metal casting, welding and brazing operations; as etching agents in glass and ceramics industries; as cleaners in metal finishing processes; in pesticides; in fluoridation of water supplies and in toothpaste and other dental preparations (Drury et al. 1980).

The fluorination of organic compounds amounted to about 108,000 metric tons in 1977 (Drury et al. 1980) and is the greatest single end use of fluorides. Hydrogen fluoride is used in the synthesis of dichlorodifluoromethane, trichlorofluoromethane, tetrafluoromethane, tetrafluoroethylene, vinyl fluoride and hexafluoropropene. These compounds are used chiefly for aerosol propellants, refrigerants and fluorinated plastics. Small quantities of other fluorocarbons find specialized uses as inhalation anesthetics, fire extinguishing agents, cleaners and degreasers (Drury et al. 1980).

Sodium fluoride is widely used in fluxes, for fluoridation of water supplies, in dentifrices and other dental preparations and for scrubbing HF from fluorine. It is also occasionally used as an insecticide and a wood preservative (Drury et al. 1980).

Fluorosilicic acid (H_2SiF_6) is sometimes used in hardening cement, preserving timber, manufacturing enamels and preserving oil pigments. A small amount of sodium fluorosilicate is used as insecticide (Drury et al. 1980).

Fluorides are emitted into the atmosphere as a result of the manufacture of fertilizer and phosphorus from rock phosphate, the operation of aluminum- and steel-producing furnaces, the manufacture of brick and tile products and the combustion of coal. The fluorides are generally in the form of HF, fluorine, boron trifluoride, H_2SiF_6, sodium fluorosilicate, aluminum fluoride, calcium fluoride, lead difluoride, fluorapatite, silicon tetrafluoride and fluoride particulates (Drury et al. 1980).

Liquid wastes containing HF or fluoride ion (F^-) are generated in appreciable quantities by glass manufacturers, pesticide and fertilizer producers, steel and aluminum makers, metal processing industries and inorganic chemical producers (Drury et al. 1980).

C. Summary

Fluorine is highly reactive. It usually occurs as ionic or covalently bonded fluoride. The most common chemical forms are fluorspar, fluorapatite, cryolite, HF, H_2SiF_6 and fluorocarbons. Most naturally occurring forms of fluoride are insoluble or only slightly soluble in water.

The main industrial source of fluoride is the mineral fluorspar. Hydrofluoric acid is made from fluorspar and is used primarily in the production of aluminum and fluorocarbon compounds.

Fluoride occurs in most rocks and soils in concentrations of 200 to 1,000 ppm. It is a normal constituent of most natural waters in concentrations up to 0.3 ppm. The water supplies of most major United States cities naturally contain 0.02 to 0.1 ppm fluoride. Groundwater fluoride concentrations vary with the type of rock the water flows through but usually do not exceed 10 ppm.

Fluorides occur in the atmosphere from natural and industrial emissions. Most atmospheric fluorides are washed out by rainfall which may contain 0.02 to 14 ppm fluoride.

III. TOXICOKINETICS

A. Absorption

Soluble fluorides are rapidly absorbed from the gastrointestinal tract of animals and humans. Zipkin and Likins (1957) demonstrated that when rats were administered, by intubation, 0.2 mg F as NaF in solution, 86% of the dose was absorbed in 90 min. In a more definitive experiment by Zipkin and Likins (1957), single doses of 1.7 to 1.8 mg F/kg of body weight were administered by stomach tube to groups of ten male rats weighing 110 to 120 g. After 30 minutes the rats were sacrificed and the percentage of the dose remaining in the gastrointestinal tract was determined. The percentage of the dose absorbed was estimated by subtracting the percentage of the dose remaining from 100%. The fluoride was administered in several chemical forms. The readily ionizable compounds NaF, Na_2SiF_6, Na_2PO_3F and SnF_2 (all administered in solution) were absorbed to the extent of 50%, 51%, 43% and 50%, respectively during the 30 minute period. Compounds not releasing ionic fluoride were absorbed more extensively. Absorption of KPF_6 and KBF_4 was 77% and 76%, respectively.

Ericsson (1958) administered 0.08 mg F (labelled with ^{18}F) per kg of body weight to groups of six male rats weighing 269 to 289 g. The fluoride was administered by stomach tube as 5 mL of an aqueous solution containing 1 ppm F (1 mg F/L). The percentage of the dose per mL of heart blood was maximal (approximately 0.18%/mL) 45 minutes after administration. Analysis of the gastrointestinal tract for fluoride remaining after eight to ten hours showed that 89% to 90% had been absorbed.

A number of studies are available describing the absorption of fluoride in humans. For example, Ekstrand et al. (1977) measured plasma fluoride concentrations after oral administration of 4.5, 6.0 or 10.0 mg F to eight subjects (six males and two females) 23- to 29-years-old. The fluoride was administered as tablets or in gelatin capsules with water. In all cases, the maximum plasma fluoride concentrations occurred within 30 minutes of administration. In a similar study, 0.5 mg F as NaF tablets was ingested with water by five children three- to four-years-old and weighing 15.5 to 17.8 kg (Ekstrand et al. 1983). Plasma fluoride concentrations were measured at 0, 30 and 60 minutes after administration. As in adults, maximum plasma fluoride concentrations were observed 30 minutes after ingestion.

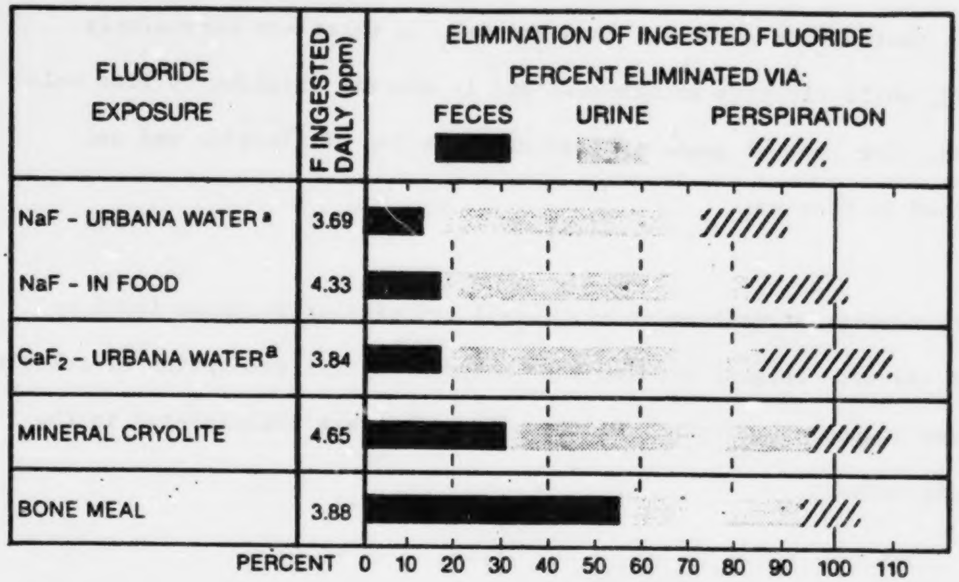
The concordance among these studies suggests the rat is an adequate model for the short-term pharmacokinetics of fluoride in humans. In summary, soluble fluoride ingested by the human is absorbed from the gastrointestinal tract at least to the extent of 97%. Absorption is rapid with maximum plasma fluoride concentrations attained in approximately 30 minutes in the human as well as in the rat.

Carlson et al. (1960a) studied the absorption of fluoride in humans. Subjects consumed 1 mg fluoride (as NaF containing ^{18}F) in 250 mL water. Maximum plasma concentrations (0.13 to 0.17 mg/L) were reached within 60 minutes. At 150 minutes ^{18}F was no longer present in the stomach. The gastrointestinal absorption of fluoride in five men 19- to 27-years-old was studied by McClure et al. (1945). Fluoride balances were determined over five-day periods while their normal diets (containing 0.50 to 0.90 mg fluoride/day, or 0.007 to 0.013 mg/kg/day for a 70-kg individual) were supplemented with NaF in water, NaF in food, CaF_2 in water, CaF_2 in food, bone meal in food or cryolite in food. Figure III-1 shows the fluoride balances associated with the various forms of fluoride exposure. Fecal excretion suggests that NaF in water and food and CaF_2 in water are extensively absorbed, while fluoride in bonemeal and in mineral cryolite is less well absorbed. The role of gastrointestinal secretion of fluoride was not determined in this work.

The results of McClure et al. (1945) are similar to those found by Largent (1960). Largent studied the gastrointestinal absorption of soluble fluorides in human subjects. Soluble fluorides were administered in the following manner:

- NaF, 2 to 4% in aqueous solution.
- CaF_2 in aqueous solution and as the dry salt in capsules.
- Bone meal as a slurry in an aqueous medium and as the dry material in capsules.
- Cryolite as a solid in capsules.
- Finely powdered fluorapatite (rock phosphate) in capsules.

Complete fluoride balance data were collected. Total fluoride intake during these studies ranged from 3.49 to 22.3 mg/day (0.05 to 0.32 mg/kg/day for a 70-kg individual). Normal dietary intake of fluoride during these studies ranged from 0.4 to 0.8 mg/day (0.006 to 0.012 mg/kg/day). Approximately 96% to 97% of the fluoride from aqueous solutions containing NaF



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[a] Urbana water was the local tap water.

Adapted from McClure et al. (1945).

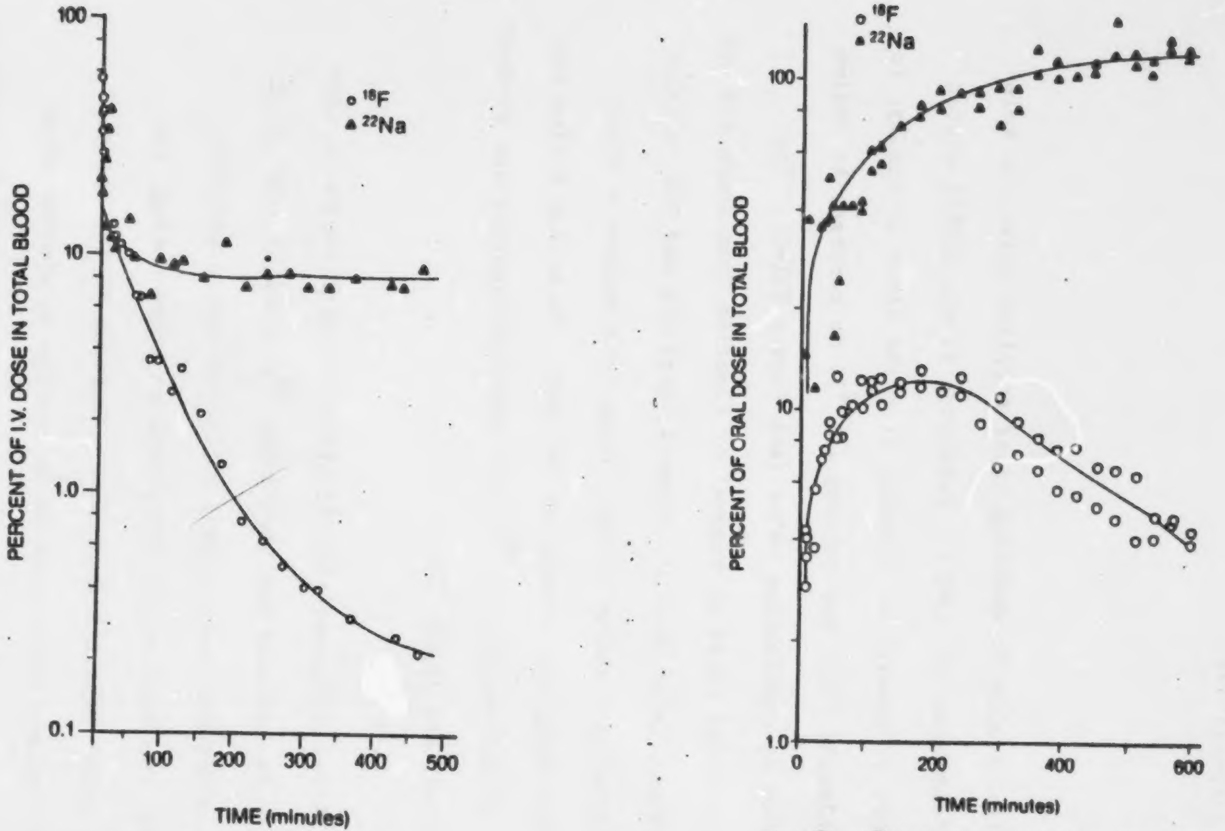
Figure III-1 Fluoride Balances in Men During Five-Day Experimental Period

or CaF_2 was absorbed. Absorption of fluoride from calcium fluoride, bone meal, cryolite and rock phosphate, administered as solids, was approximately 62%, 37%, 77% and 87%, respectively.

B. Distribution

Fluoride added intentionally to drinking water supplies exists in solution as fluoride ion (Feldman et al. 1957). Perkinson et al. (1955) stated that the rate and pattern of removal of fluoride from the blood is similar to that of ions such as chloride (Cl^-) and calcium (Ca^{+2}), in contrast to sodium (Na^+), which soon reaches an equilibrium value (see Figure III-2). The authors found that the initial rates of removal of fluoride from sheep and cow blood (expressed as percentage of dose per minute), were 41% and 32%, of the intravenously administered dose respectively. These data suggest a rapid distribution of fluoride among the tissues of the body. In a lamb killed two hours after ingestion of NaF containing ^{18}F, the absorbed fluoride was in fact found to be widely distributed (Table III-1).

Carlson et al. (1960a) indicated that distribution of fluoride is also rapid in humans. Subjects consumed NaF containing ^{18}F in water (250 mL at 1 mg/L). Epigastric (abdominal) counts were monitored with a portable scintillation counter. One hundred and fifty minutes after dosing, the remaining epigastric counts were attributable to fluoride in the spine. Counts in muscle (contracted biceps) started to decline 50 minutes after ingestion, until at 250 minutes they were nearly zero. In contrast, counts in the femur had declined only 15% from their maximum value (at 50 minutes) by 250 minutes.



Disappearance of ^{18}F and ^{22}Na from blood of lamb after intravenous administration

Blood ^{18}F and ^{22}Na after oral administration of radioactive sodium fluoride to lambs

Adapted from Perkinson et al. (1955).

Figure III-2 Concentrations of ^{18}F and ^{22}Na in Blood after Intravenous and Oral Administration of Radioactive Sodium Fluoride to Lambs

Table III-1 ^{18}F Distribution in a Lamb Killed Two Hours After Ingestion[a]

Blood	0.00061	Rib epiphysis	0.0048
Bile	0.00050	Rib shaft	0.0018
Muscle	0.00015	Femur epiphysis	0.0046
Spleen	0.00016	Femur shaft	0.0008
Pancreas	0.00033	Angle of mandible	0.0045
Lymph node	0.00028	Molar tooth	0.0010
Liver	0.00033		

[a] Values in percentage of dose per gram fresh weight.

Adapted from Perkinson et al. (1955).

C. Metabolism

Bone is formed when calcium and phosphorus are deposited on a collagen matrix (Kay et al. 1964). The resultant mineral phase is known as hydroxyapatite and has the formula $Ca_{10}(PO_4)_6(OH)_2$. Fluoride is believed to replace the hydroxyl ion (OH^-) and possibly the bicarbonate ion (HCO_3^-) associated with normal hydroxyapatite (Neuman et al. 1950, McCann and Bullock 1957). The resultant material is called fluorohydroxyapatite, or simply fluorapatite. Kay et al. (1964) analyzed the crystal structure of hydroxyapatite using neutron diffraction and X-ray diffraction techniques. Their data indicated that the OH^- of hydroxyapatite is in a less stable configuration than the F^- of fluorapatite. This might explain the ability of fluoride to harden bone and to increase the resistance of teeth to caries.

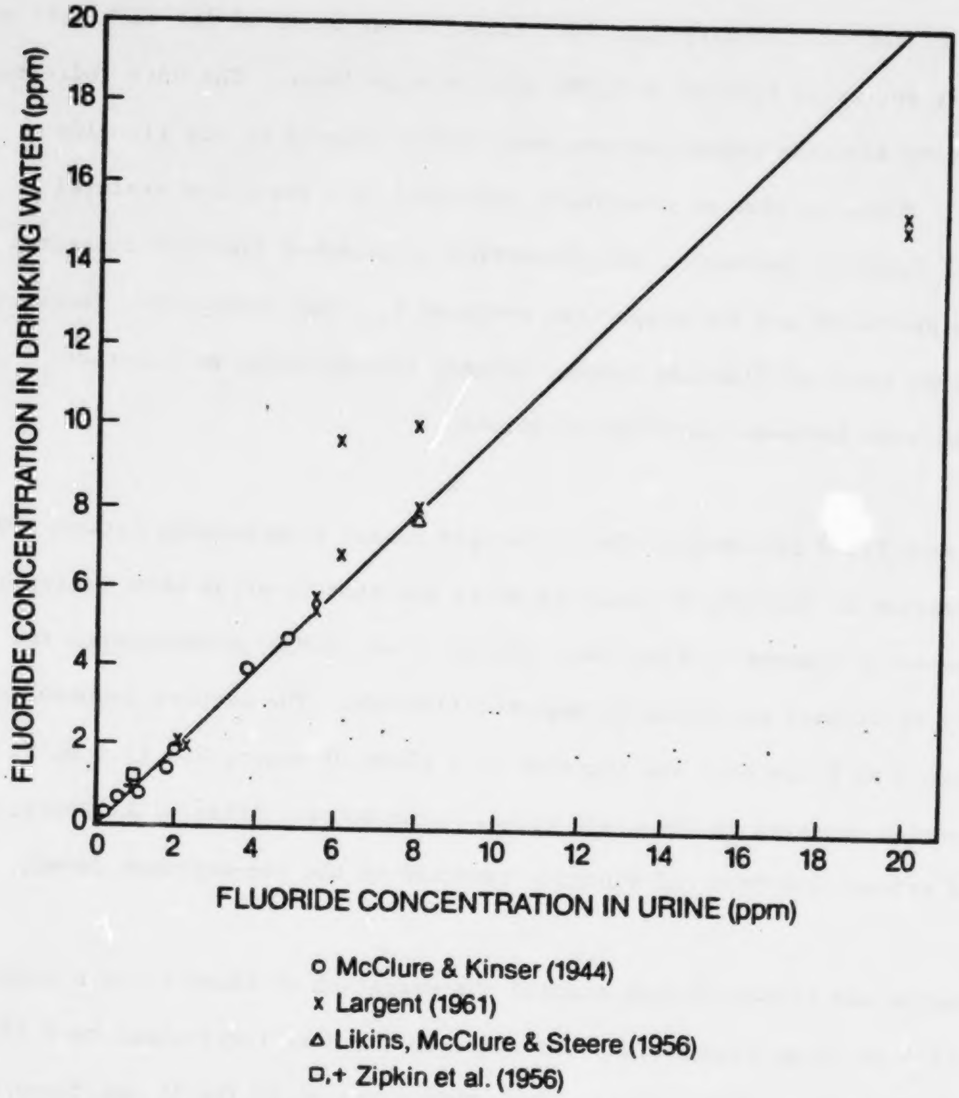
D. Excretion

The principal route of excretion of ingested fluoride is via the urine, as has been demonstrated in a variety of species. However, in species other than man, there is little published data relating fluoride concentrations in drinking water and in urine over prolonged periods of time. Several studies on livestock have been reported. For example, Shupe et al. (1963) fed pairs of dairy cattle rations containing 12 (normal), 27, 49, or 93 ppm fluoride on a total dry matter basis from about 4 months to 7.5 years of age. Each pair of animals also received one of two levels of calcium-phosphorus mineral and one of two levels of concentrate mix. The total population consisted of

16 pairs of cattle. Urinary fluoride excretion was measured for each pair of animals at intervals from 89 to 2,396 days on experiment. The data indicated that urinary fluoride concentrations were highly related to the fluoride ingested. Also, as time on experiment increased, and therefore skeletal stores of fluoride increased, the proportion of absorbed fluoride deposited in the bone decreased and the proportion excreted in urine increased. Therefore, for a given level of fluoride intake, urinary concentration of fluoride increased with increased duration of intake.

Figure III-3 illustrates the strikingly linear relationship between the concentration of fluoride in drinking water and that in urine when individuals are constantly exposed to fluoride. Zipkin et al. (1957) demonstrated the rapidity of urinary excretion of ingested fluoride. The authors demonstrated that when 5 mg F (as NaF) was ingested in a glass of water, 20% (1.6 mg F) of the fluoride appeared in the urine within three hours. After eight hours, the rate of urinary excretion of fluoride returned to the pre-exposure level.

Machle and Largent (1943) studied the excretion of fluoride in a human subject; 6 to 19 mg fluoride/day was added to the diet (equivalent to 0.19 to 0.6 mg/kg/day for a 70-kg adult). Over this range of intake it was found that about half of the absorbed fluoride was excreted in the urine. Using fluoride labeled with ^{18}F, Carlson et al. (1960a) demonstrated that in two human subjects 51% and 63% of the fluoride filtered by the kidney was reabsorbed. In contrast, at least 99.5% of filtered chloride is reabsorbed in a normal individual. The relative inefficiency of the human kidney in reabsorbing filtered fluoride accounts for the rapid urinary excretion of fluoride.



Adapted from WHO (1970)

Figure III-3 Relation Between Fluoride Concentrations in the Urine of Humans and That in the Water Supplies Used

In climates with warm temperatures a significant fraction of total fluoride excretion may be via perspiration. McClure et al. (1945) measured excretion of fluoride in the perspiration of individuals maintained for eight-hour periods in "comfortable" conditions (temperature 84 to 85°F, relative humidity 49% to 52%) and in "hot-moist" conditions (temperature 100-101°F, relative humidity 66% to 70%). Under the "comfortable" conditions about 25% of the fluoride excreted per day appeared in perspiration. Under the "hot-moist" conditions up to 46% of the excreted fluoride was in perspiration. Hodge et al. (1970) have pointed out that the importance of this route of excretion under different climactic conditions cannot yet be stated due to a lack of information.

E. Bioaccumulation and Retention.

In the body, the only significant covalent interaction of fluoride is with the hydroxyapatite in bones and teeth. Consequently, soft tissue concentrations of fluoride rise transiently after ingestion of fluoride (Carlson et al. 1960b, Hein et al. 1956), but long-term retention and accumulation are confined to calcified tissue (Wagner et al. 1958). Suttie et al. (1958) measured soft tissue concentrations of fluoride in 20 heifers exposed to 0 to 50 ppm (equivalent to 1.4 mg/kg/day) added fluoride in their ration for 5.5 years. Control animals (0 ppm added fluoride in their ration) had soft tissue fluoride concentrations from 2.1 ppm (thyroid) to 5.3 ppm (adrenal) and an average whole blood fluoride concentration of 0.34 ppm. Heifers exposed to 50 ppm (equivalent to 1.41 mg/kg/day) added fluoride in their ration had soft tissue fluoride concentrations from 4.2 ppm (pancreas) to 19.3 ppm (kidney), dry weight, and an average whole blood fluoride concentration 0.67 ppm. It should be noted that the kidney is an important route of excretion for fluoride. Data on soft tissue storage of fluoride are summarized in Table III-2.

Twenty heifers exposed to 0, 20, 30, 40 and 50 ppm added fluoride (ingested as NaF; equivalent to 0, 0.53, 0.86, 1.03 and 1.36 mg/kg/day, respectively) in their ration for 5.5 years showed progressive increments in bone fluoride concentration corresponding to the amounts of added fluoride (Suttie et al. 1958). Some samples of bone from animals exposed to 50 ppm added fluoride (equivalent to 1.36 mg/kg/day) in their ration contained more than 8,000 ppm fluoride on a fat-free dry weight basis. The data from this report are summarized in Table III-3.

The deposition of fluoride in the skeleton of female Holtzman rats was studied by Suttie and Phillips (1959). Three age groups, weanlings, young adults (10-weeks-old) and mature rats (18-weeks-old), were started on a diet containing 0.1% NaF. Rats were sacrificed at various times up to 113 days after the start of the exposure to fluoride. At sacrifice, femurs were removed and analyzed for fluoride. The results of this study are summarized in Figure III-4. These data show that after an initial phase of rapid uptake of fluoride into bone, the rate of uptake gradually diminishes. Moreover, the concentration of fluoride in bone at the end of the experiment was inversely correlated with the initial ages of the rats. The authors believed that this

Table III-2 The Effect of Added Dietary Increments of Fluoride Ion (NaF) on Soft Tissue Fluoride Concentrations in Dairy Cows

			Tissue Levels[a]						
Lot	F Added (ppm)	Cow No.	Heart[b]	Liver[b]	Kidney[b]	Pancreas[c]	Thyroid[c]	Adrenal[c]	Blood[d]
I	0	2	1.8	3.1	3.1	1.7	0.6	2.0	0.49
		3	3.3	1.9	2.9	4.0	2.7	11.9	0.32
		4	1.7	1.9	4.4	2.0	2.9	2.2	0.22
		Av.	2.3	2.3	3.5	2.8	2.1	5.3	0.34
II	20	5	2.7	2.4	7.3	1.4	2.9	3.8	0.34
		6	4.4	2.1	6.0	2.6	7.0		0.59
		7	2.5	2.3	8.3	3.2	6.6		0.84
		8	4.0	3.9	12.8	1.7	11.2	3.3	0.39
		Av.	3.4	2.7	8.6	2.2	6.9	3.5	0.54
III	30	10	2.7	2.5	12.5	2.0	2.4	3.3	0.45
		11	4.7	4.6	9.1	5.0	4.1		0.89
		12	3.0	5.1	10.5	3.5	4.1	3.3	0.30
		Av.	3.5	4.1	10.7	3.5	3.5	3.3	0.55
IV	40	13	3.3	5.6	19.7	3.0	4.9	2.5	0.94
		14	5.5	3.3	20.4	5.1	5.0	3.5	0.69
		15	4.5	3.4	7.8	-	-	-	-
		16	2.9	3.0	16.0	3.4	7.6	8.8	0.31
		Av.	4.0	3.8	16.0	3.8	5.8	4.7	0.66
V	50	17	5.0	2.3	13.7	4.5	5.2	8.7	0.38
		19	3.2	2.1	15.4	4.1	12.2		0.78
		20	6.3	4.8	28.9	4.0	4.4	4.1	0.84
		Av.	4.6	3.6	19.3	4.2	7.3	6.4	0.67
VI	50 + $CaCO_3$	22	3.8	3.5	11.1	3.6	4.2		1.10
		23	4.6	2.7	7.7	3.5	4.9	4.2	0.68
		24	5.6	2.8	8.4	3.0	9.0	4.1	0.88
		Av.	4.6	3.0	9.0	3.4	6.0	4.1	0.89

[a] All values in ppm.
[b] Dry weight.
[c] Dry, fat-free weight.
[d] Whole blood.

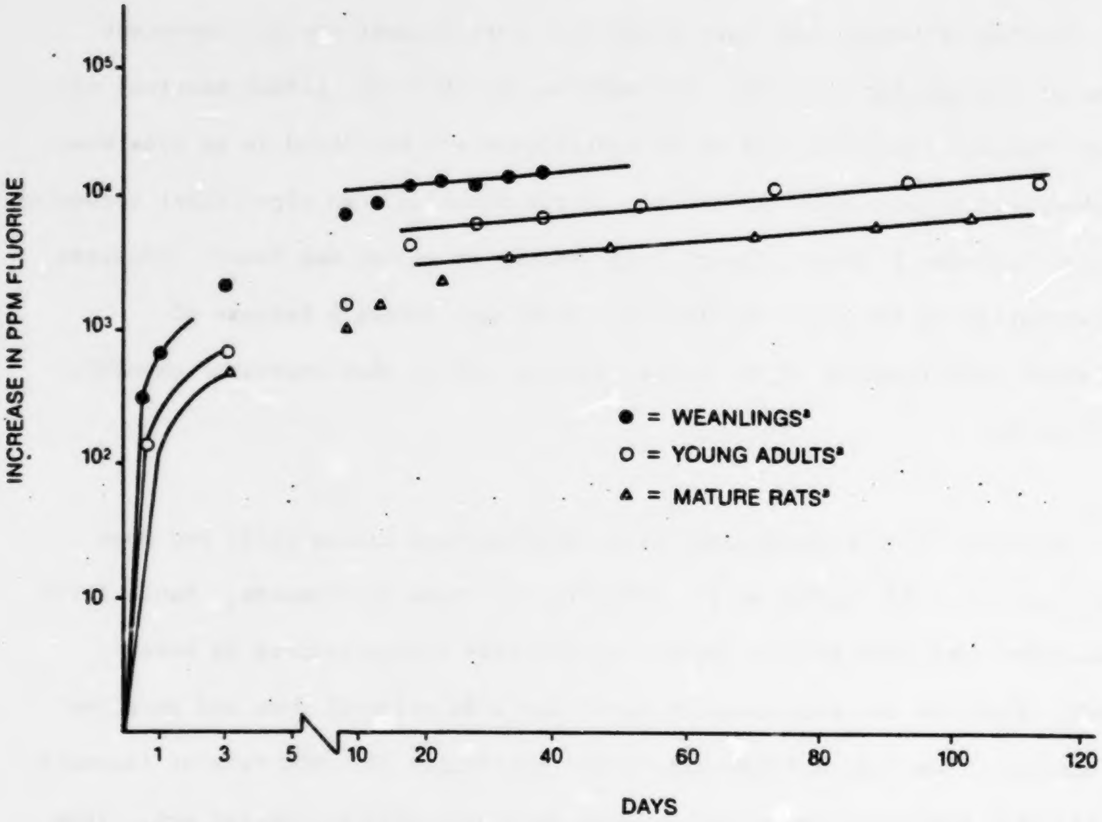
Adapted from Suttie et al. (1958).

Table III-3 The Effects of Added Dietary Increments of Fluoride Ion (NaF) on Bone Fluoride Concentrations in Dairy Cows[a]

Lot	F Added (ppm)	Cow No.	Bone Concentrations[b] Meta-carpal	Meta-tarsal	Frontal	12th Rib
I	0	2	593	482	647	694
		3	878	647	701	635
		4	463	436	592	703
		Av.	645	522	645	677
II	20	5	2720	2610	3200	3290
		6	2770	2990	3340	4770
		7	2170	2610	3110	4030
		8	2660	3030	3430	3910
		Av.	2580	2810	3270	4000
III	30	10	4180	4090	4540	4900
		11	3780	3310	4920	5970
		12	4120	4200	4800	5280
		Av.	4030	3870	4750	5380
IV	40	13	5520	5280	6180	7030
		14	5840	5380	6010	7070
		15	4510	4710	--	4100
		16	3740	3180	4730	4860
		Av.	4900	4640	5640	5770
V	50	17	7610	7800	8260	9000
		19	5470	4920	6800	8100
		20	4050	4360	6700	6870
		Av.	5710	5690	7250	7990

[a] Concentrations expressed as ppm flouride.
[b] Dry fat-free weight.

Adapted from Suttie et al. (1958).



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*Each point is the mean of three animals.

Adapted from Suttie and Phillips (1959).

Figure III-4 The Effect of Age on the Rate of the Increase of Fluorine Concentration in the Femur of the Rat

difference was related to the surface area per mass of bone which could be reached by body fluids. Thus, adult bone is more fully mineralized while the infant bone is new, hydrated and available for fluoride exchange.

Studies of humans have also shown that soft tissues are not important sites of storage for fluoride. For example, Smith et al. (1960) examined 122 tissue samples from autopsies of 23 individuals who had lived in an area where drinking water contained from 1.0 to 4.0 ppm fluoride. No significant accumulation of fluoride in heart, liver, lung, kidney or spleen was found. Fluoride concentration in the aorta did increase with age, probably because of increased calcification of the aorta with age rather than increased exposure to fluoride.

In contrast to soft tissues, teeth (McClure and Likins 1951) and bone (Smith et al. 1953, Suttie et al. 1958) readily take up fluoride. Table III-4 summarizes data from several reports on fluoride concentrations in human teeth. Fluoride concentrations in teeth are a function of dose and duration of exposure. Jackson and Weidmann (1959) determined that the rate of increase of fluoride concentration in human teeth decreases with increasing age. This study demonstrated that in West Hartlepool, an English city with a drinking water fluoride concentration of 2.0 ppm, the fluoride content of tooth enamel varied with age in the following manner: 5- to 11-years-old, 17±0.9 mg fluoride/100 g enamel; 20- to 35-years-old, 32±0.28 mg/100 g; 50- to 73-years-old, 37±7.5 mg/100 g.

Table III-4 Fluoride Concentrations (Expressed as ppm in Ash) in Dentine and Enamel at Different Levels of Fluoride Ingestion[a]

			Fluoride in Ash (ppm)			
			Enamel			Dentine
Reference	Age	Dose[b]	surface	interior	whole	whole
McClure & Likins (1951)	Adult	0.1	--	--	86	332
		7.6	--	--	658	1958
Jackson & Weidmann (1959)	20-49 yr	<0.5	--	--	108	508
	20-35 yr	1.2	--	--	180	922
	20-35 yr	1.9	--	--	320	1290
Jenkins & Speirs (1953)	Adult	<0.25	590	80	--	--
		1.4	960	110	--	--
		2.0	1310	270	--	--
Brudevold, Steadman & Smith (1960)	20-29 yr	0.1	571	48	--	--
		1.0	889	129	--	--
		3.0	1930	152	--	--
		5.0	3370	570	--	--

[a] All data for humans and lifelong exposures.
[b] Dose in ppm fluoride in water.

Adapted from WHO (1970).

Zipkin et al. (1958) studied fluoride concentrations in the bones of humans exposed to fluoride in drinking water at concentrations from 0.1 ppm (New York City) to 4.0 ppm (Lubbock, Texas). The authors found a linear relationship between the concentration of fluoride in water and the concentration in bone. This study was not analyzed to account for the amount of time that individual subjects had lived in the designated areas.

The concentration of fluoride in human bone also increases with duration of exposure. Smith et al. (1953) found a linear relationship between age in years and concentration of fluoride in bone ash from lifetime residents of an area with a drinking water supply containing approximately 0.06 ppm fluoride. Fluoride concentrations as high as 1,300 ppm were observed in bone ash. Jackson and Weidman (1958) analyzed levels of fluoride in bone from residents of three English cities with different concentrations of fluoride in their drinking water: West Hartlepool, 1.9 ppm; South Shields, 0.8 ppm; and Leeds, less than 0.5 ppm. In each case, a plateau in bone fluoride concentration appeared at about age 55. The parameters influencing whether or not concentrations of fluoride in human bone plateau with increasing age are not understood (NAS 1971). In view of the large intersubject variability, there may not be a true plateau. Also, at only 0.1 ppm fluoride in the water, a plateau may not be reached in a lifetime.

Machle and Largent (1943) showed that when adult humans absorbed up to 18 mg of fluoride per day, about half of this amount was deposited in the skeleton. The fraction of the absorbed dose of fluoride deposited in the skeleton of younger persons is somewhat greater. For example, Zipkin et al. (1956) measured concentrations of urinary fluoride in children and in adults before and after fluoridation of a community water supply. In the adults, urinary fluoride concentration equaled that of the fluoridated drinking water after one week. In the children, three years passed before the fluoride concentration in urine approximated that of the ingested drinking water.

In quasi-steady state conditions of fluoride intake, a corresponding skeletal concentration of fluoride is reached which then continues to increase slowly with time. The skeletal concentration is related directly to the level of steady state intake. The rate of uptake and retention in the bone declines with age, but whether or not concentrations in the bone reach a plateau commensurate with the daily intake cannot yet be stated with certainty. When intake is elevated above "normal" amounts, either briefly or perhaps over several weeks, approximately half of the additional absorbed fluoride will be deposited in the bone. Upon reestablishing the "normal" steady state, the excess fluoride retained in the bone also declines. There is no significant accumulation or retention of fluoride in soft tissues.

F. Summary

Following ingestion, soluble fluorides are rapidly absorbed from the gastrointestinal tract at least to the extent of 97%. Absorbed fluoride is distributed throughout the tissues of the body by the blood. Fluoride concentrations in soft tissues fall to pre-exposure levels within a few hours of exposure. Fluoride exchanges with hydroxyl radicals of hydroxyapatite (the inorganic constituent of bone) to form fluorohydroxyapatite. Fluoride that is not retained is excreted rapidly in urine. In adults under steady state intake conditions, the urinary concentration of fluoride tends to approximate the concentration of fluoride in the drinking water. This reflects the decreasing retention of fluoride (primarily in bone) with increasing age. Under certain conditions perspiration may be an important route of fluoride excretion. The concentration of fluoride retained in bones and teeth is a function of both the concentration of fluoride intake and the duration of exposure. Periods of excessive fluoride exposure will result in increased retention in the bone. However, when the excessive exposure is eliminated, the bone fluoride concentration will decrease to a concentration that is again reflective of intake.

IV. HUMAN EXPOSURE

Humans can be exposed to fluoride in drinking water, food and air (Letkiewicz 1984). This section summarizes available pertinent information in order to assess the relative source contribution of fluoride from drinking water, food and air.

A. Exposure Estimation

This analysis is limited to drinking water, food and air since these media are considered general sources of fluoride for all individuals. Some individuals may be exposed to fluoride from other sources, notably in occupational settings and from the use of consumer products containing fluoride. In limiting the analysis to these three sources, it must be recognized that individual exposure can vary widely based on several uncontrollable factors. Life style, food consumption and physiological characteristics (age, sex and health status) can all affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided giving the number of individuals exposed to each medium at various fluoride concentrations.

B. Drinking Water Exposure

It is estimated that over 86% of the 195,595,000 people using public water supplies are exposed to fluoride at levels of 1.0 mg/L or less; most (77.6%) are receiving water containing fluoride at levels of 0.1 to 1.0 mg/L. Approximately 835,000 people in the U.S. are exposed to drinking water levels exceeding 2.0 mg/L. Approximately 90% of those exposed to fluoride at levels above 2.0 mg/L receive their drinking water from groundwater sources (Table IV-1).

Table IV-2 presents the estimated daily intake of fluoride from drinking water for three population groups (adult males, 5- to 13-year-old children and newborn formula-fed infants) as a function of the fluoride levels in drinking water. The data indicate that, on a per body weight basis, the drinking water intake of fluoride by children in the 5 to 13 age group is approximately 1.4 times that of the adult male. The intake of newborn formula-fed infants is more than eight-times that of adult males. The drinking water intake calculations used here do not include the factor for air temperature that is allowed for in the existing EPA and PHS standards. The basis for that relationship has recently been questioned (Coniglio 1984) and revised drinking water regulations are not expected to incorporate such a factor in the Maximum Contaminant Level (MCL).

Table IV-1 Estimated Population Exposed to Fluoride in Drinking Water at Various Concentration Ranges

System Type	Number of people served in U.S. (thousands)	Number of people (thousands) exposed to fluoride at concentrations (mg/L) of:									
		<0.1	0.1-1.0	>1.0-2.0	>2.0-3.0	>3.0-4.0	>4.0-5.0	>5.0-6.0	>6.0-7.0	>7.0-8.0	>8.0
Groundwater	69,239	3,067	61,552	3,872	408.9	163.1	105.5	56.1	9.3	2.0	3.2
Surface water	126,356	13,548	90,132	22,590	71.8	6.0	5.1	0.04	2.7	0.4	0.08
Total	195,595	16,615	151,684	26,462	481	169	111	56	12	2.4	3.2
(% of total)	(100%)	(8.5%)	(77.6%)	(13.5%)	(0.2%)	(0.1%)	(<0.1%)	(<0.1%)	(<0.1%)	(<0.1%)	(<0.1%)

Table IV-2 Estimated Intake of Fluoride from Drinking Water

Fluoride concentration in drinking water (mg/L)	Approximate percent of population exposed to fluoride in drinking water at the indicated concentration range	Drinking water intake per individual[a] (mg/kg/day)		
		Adult males[b]	Children (5-13 year-old)[c]	Newborn Formula-fed infants[d]
0-2	99.6%	2.9×10^{-2}	4.2×10^{-2}	2.4×10^{-1}
> 2-4	0.3%	8.6×10^{-2}	1.3×10^{-1}	7.3×10^{-1}
> 4-6	< 0.1%	1.5×10^{-1}	2.1×10^{-1}	1.2
> 6-8	< 0.01%	2.0×10^{-1}	3.0×10^{-1}	1.7
> 8	<< 0.01%	2.9×10^{-1}	4.2×10^{-1}	2.4

[a] Calculations based on the midpoint of the indicated concentration range except for > 8 mg/L range, which uses 10 mg/L for the drinking water level; assumes 100% absorption.

[b] Calculation based on an adult male weighing 70 kg consuming 2 L of water per day.

[c] Calculation based on a 10 year-old child weighing 33 kg consuming 1.4 L of water per day.

[d] Calculation based on an infant weighing 3.5 kg consuming 0.8 L of formula per day.

C. Dietary Exposure

Several estimates have been made of the daily dietary intake of fluoride in the United States (exclusive of drinking water). These are shown in Table IV-3. These estimates generally place fluoride dietary intake in the range of 0.2 to 0.8 mg/day.

In contrast, Osis et al. (1974) reported a higher daily dietary intake of fluoride at 1.6 to 1.9 mg over a 6-year period in an area with a fluoridated water supply. Kramer et al. (1974) reported fluoride dietary intakes of 1.7 to 2.4 mg/day in 12 cities using fluoridated water. In four cities using nonfluoridated water the intake was 0.8 to 1.0 mg/day. Both of these studies used a method of analysis reported by Singer and Armstrong (1965). However, Singer et al. (1980) indicated that the method used in those studies would lead to an overestimation of fluoride. While these values may not be quantitatively valid, it is interesting to note that Kramer et al. (1974) provided useful data on the correlation of dietary levels observed in the various cities with the level of fluoridation of drinking water. While no direct correlation was observed for individual cities, the mean dietary level in fluoridated cities was about three times that of the nonfluoridated cities, and the mean fluoride content of the drinking water in fluoridated cities was also about three times that of non-fluoridated cities.

Table IV-3 Reported Daily Dietary Intake of Fluoride
(exclusive of water)

Source	Category of Individual	Daily Intake (mg)
WHO (1970)	Age 1 - 3	0.027 - 0.265
	4 - 6	0.036 - 0.360
	7 - 9	0.045 - 0.450
	10 - 12	0.056 - 0.560
NAS (1980)	Adult	0.2 - 0.3
Underwood (1973)	Adult	0.3 - 0.5
Hodge and Smith (1970)	Adult	0.3 - 0.8
Singer et al. (1980)[a]	Young adult male (age 16 - 19)	0.333 (San Francisco) 0.378 (Buffalo) 0.587 (Atlanta) 0.368 (Kansas City)

[a] Excludes all beverages.

D. Air Exposure

The information on levels of fluoride in air suggest that airborne fluoride contributes little to total daily intake. Assuming that an adult male inhales 23 m^3 air/day and absorbs 100% of the inhaled fluoride, airborne fluoride present at the usual limit of detection (0.05 μg/m^3) would contribute about 1.2 μg/day to an individual's intake. This is to be compared to the estimated values of 200 to 800 μg/day for food and drinking water.

E. Summary

Table IV-4 shows the relative source contribution of food, air and drinking water for the daily fluoride intake for an adult male in the United States. The predominant sources of fluoride for the adult male in the United States are food and drinking water. Typical air levels of fluoride are extremely low. Most fluoride air levels are below the limits of detection, usually 0.05 μg/m^3. Fluoride at 0.05 μg/m^3 would, with 100% absorption, contribute only 1.2 μg/day to an adult male's daily intake (23 m^3/day respiration volume is assumed). For an adult male weighing 70 kg, the corresponding air dose is 1.7×10^{-5} mg/kg/day. The air contribution appears to be negligible except when food and drinking water doses are zero.

The food intake shown was derived from the data presented in Letkiewicz (1984), which suggested that the daily dietary intake was 0.2 to 0.8 mg/day. Assuming 100% absorption for a 70-kg adult male, these values correspond to 2.9×10^{-3} to 1.1×10^{-2} mg/kg/day.

Table IV-4 Estimated Intake of Fluoride from the Environment by Adult Males[a]

Fluoride concentration in drinking water (mg/L)	Estimated percent of the population exposed to indicated fluoride concentration range from public water supplies (% of total)	Drinking water intake per individual[b] (mg/kg/day)	Total intake per individual in mg/kg/day (% from drinking water)			
			Food intake per individual[c] (mg/kg/day):	2.9×10^{-3}	7.1×10^{-3}	1.1×10^{-2}
0-2	99.6%	2.9×10^{-2}		3.2×10^{-2} (91%)	3.6×10^{-2} (81%)	4.0×10^{-2} (72%)
> 2-4	0.3%	8.6×10^{-2}		8.9×10^{-2} (97%)	9.3×10^{-2} (92%)	9.7×10^{-2} (89%)
> 4-6	< 0.1%	1.5×10^{-1}		1.5×10^{-1} (98%)	1.6×10^{-1} (95%)	1.6×10^{-1} (93%)
> 6-8	< 0.01%	2.0×10^{-1}		2.0×10^{-1} (99%)	2.1×10^{-1} (97%)	2.1×10^{-1} (95%)
> 8	<< 0.01%	2.9×10^{-1}		2.9×10^{-1} (99%)	3.0×10^{-1} (98%)	3.0×10^{-1} (96%)

[a] Daily intake from air (estimated to be less than 1.7×10^{-5} mg/kg/day) considered negligible relative to food and drinking water.

[b] Calculation based on an adult male weighing 70 kg consuming 2 L of water per day and using the midpoint of the indicated concentration range except for the > 8 mg/L range, which uses 10 mg/L for the drinking water level.

[c] Based on data showing the daily adult dietary intake of fluoride ranging from 0.2-0.8 mg/day and a 70-kg adult (2.9×10^{-3} mg/kg/day = 0.2 mg/day; 7.1×10^{-3} mg/kg/day = 0.5 mg/day; 1.1×10^{-2} mg/kg/day = 0.8 mg/day).

Under the typical drinking water exposure condition of about 1.0 mg/L, drinking water accounts for an estimated 72% to 91% of total fluoride intake for the adult male, with food contributing the remainder. Where drinking water levels exceed 2 mg/L, the contribution from drinking water is generally expected to exceed 90% of total intake.

A similar comparison of relative source contribution is shown in Table IV-5 for 5- to 13-year-old children. As in the case of the adult male, the contribution from air is negligible relative to drinking water and food. Under the typical drinking water exposure condition of about 1.0 mg/L, drinking water accounts for 64% to 97% of total fluoride intake. Where drinking water levels exceed 2.0 mg/L, drinking water accounts for more than 90% of total intake.

Table IV-5 Estimated Intake of Fluoride from the Environment by 5-13 year-old Children[a]

Fluoride concentration in drinking water (mg/L)	Estimated population of 5-13 year-old children exposed to indicated fluoride concentration range from public water supplies[b]	Drinking water intake per individual[c] (mg/kg/day)	Total intake per individual in mg/kg/day (% from drinking water)			
			Food intake per individual[d] (mg/kg/day):	1.1×10^{-3}	1.3×10^{-2}	2.4×10^{-2}
0-2	26,039,600	4.2×10^{-2}		4.3×10^{-2} (97%)	5.5×10^{-2} (76%)	6.6×10^{-2} (64%)
> 2-4	86,800	1.3×10^{-1}		1.3×10^{-1} (99%)	1.4×10^{-1} (91%)	1.5×10^{-1} (84%)
> 4-6	22,300	2.1×10^{-1}		2.1×10^{-1} (99%)	2.2×10^{-1} (94%)	2.3×10^{-1} (90%)
> 6-8	1,900	3.0×10^{-1}		3.0×10^{-1} (100%)	3.1×10^{-1} (96%)	3.2×10^{-1} (93%)
> 8	400	4.2×10^{-1}		4.2×10^{-1} (100%)	4.3×10^{-1} (97%)	4.4×10^{-1} (96%)

[a] Daily intake from air (estimated to be less than 2.3×10^{-5} mg/kg/day) considered negligible relative to food and drinking water.

[b] Based on 1981 data provided in Statistical Abstract of the United States 1982-83 showing 13.37% of the total U.S. population falling in the 5-13 year-old age group.

[c] Calculation based on 10 year-old child weighing 33 kg consuming 1.4 L of water per day using the midpoint of the indicated concentration range except for the > 8 mg/L range which uses 10 mg/L for the drinking water level.

[d] Based on data showing the daily dietary intake of fluoride for children ages 4-12 to range from 0.036-0.56 mg/day and assuming a body weight of 33 kg (1.1×10^{-3} mg/kg/day = 0.036 mg/day; 1.3×10^{-2} mg/kg/day = 0.30 mg/day; 2.4×10^{-2} mg/kg/day = 0.56 mg/day).

V. HEALTH EFFECTS IN ANIMALS

A. Acute Toxicity

The toxicological effects of fluoride in animals are summarized below. To provide a common basis for comparison of individual studies, all dose values have been expressed in terms of milligrams fluoride per kilogram body weight (mg/kg). Where the literature provided dose information in alternative units (i.e., ppm in drinking water), the dose in terms of mg/kg has been calculated and shown parenthetically in the text.(a)

Leone et al. (1956) described the acute and subacute physiological and pathological effects of fluoride (as sodium fluoride) administered intravenously and orally to male and female dogs. When fluoride was infused intravenously in four dogs at the rate of 5.4 mg F/min, the mean acute lethal dose was 36.0 ± 0.5 mg F/kg with death occurring after 59 to 64 minutes of infusion. The principal effects observed were a progressive decline in blood pressure, heart rate, central nervous system activity (pupil size, response to light, tendon reflexes) with vomiting and defecation. All effects became

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(a) Equation for conversion of dose values from ppm in drinking water to mg/kg:

$$\text{Dose, mg/kg} = \frac{\begin{array}{c}\text{ppm in}\\ \text{drinking}\\ \text{water}\end{array} \times \dfrac{1\ \text{mg/L}}{1\ \text{ppm}} \times \begin{array}{c}\text{Daily Water}\\ \text{Consumption, L}\end{array}}{(\text{Animal Weight, Kg})}$$

evident when the infused dose reached approximately 20 mg F/kg. At a mean dose of 30.6 mg F/kg, the respiratory rate was depressed and electrocardiographic changes indicated a conversion to atrioventricular nodal or ventricular rhythm. The terminal cardiac event was either ventricular fibrillation or asystole.

In a separate study by Leone et al. (1956), dogs were infused at the rate of 5.4 mg F/min to total doses of 25, 20 and 15 mg F/kg and the animals observed until death or sacrifice. The number of dogs at each dose was 3, 2 and 4, respectively. Dogs receiving 25 mg F/kg died within 1 to 31 hrs after infusion. One of the dogs administered 20 mg/kg died after 36 hours and the second died after seven days. None of the dogs receiving 15 mg F/kg died. These animals were sacrificed 36 hrs, 7 and 16 days after infusion. The approximate LD_{50} from this study was estimated to be 20 mg F/kg. The major effects observed were vomiting, defecation and central nervous system depression.

In a third study, two dogs were administered a dose of 5 mg F/kg, infused at the rate of 1 mg F/min daily for 23 days. There were no deaths nor evidence of toxic effects or weight loss, and the electrocardiograms were normal. However, blood pressure and respiratory rate were not measured. Four dogs were also evaluated in a very limited oral study. Each dog was administered a single oral dose of sodium fluoride. The doses administered were 38, 81, 260 and 3,100 mg F/kg. The principal effects observed were vomiting and frequent defecation. Each dog appeared to recover completely within 18 to 24 hours.

During these studies by Leone et al. (1956) serum calcium levels were measured in dogs receiving total doses of 36, 25, 20 or 15 mg F/kg intravenously and in the one dog administered 3,100 mg F/kg orally. In one instance the calcium concentration increased slightly, in one instance it was unaltered, and in the remaining dogs it was lowered slightly from predosing levels. No statistically significant conclusions can be drawn from these observations. Microscopic examination of tissue reactions from all dogs dying after fluoride administration, and in one animal sacrificed 36 hours after receiving 15 mg/kg total dose, showed generalized hyperemia and acute focal hemorrhages. All other animals showed some focal hyperemia and focal hemorrhages, but these were no more severe than were seen in the control dogs.

In essence, the findings of Leone et al. (1956) provide no evidence of cumulative effects following daily administration of sublethal doses of fluoride for up to 3 weeks. The physiological effects and pathological changes seen in dogs resemble those reported for humans (Lidbeck et al. 1943). The pathological studies performed did not identify a specific mechanism of death, though direct toxic cellular effects cannot be discounted.

The acute toxicity of NaF in fasted male white mice of uniform weight (10 grams) was also studied by Leone et al. (1956). The oral LD_{50} and intravenous LD_{50} were evaluated in groups of ten or more mice. The arbitrary endpoint was 24 hours after administration. The oral LD_{50} with standard error was 46.0±1.6 mg fluoride ion/kg compared with an intravenous LD_{50} of 23.0±0.9 mg/kg. Mice dying within two hours after injection developed, successively: cyanosis, dilation of the ear vessels, depression of respiration, tremors, clonic convulsions, paralysis of the hind legs, loss of righting reflex, depression, respiratory arrest and death. Those with longer survival periods (2 to 24 hours) went through similar but less severe stages, progressing to a long terminal depression.

Maynard et al. (1951) studied the effects of age and sex on the acute lethality of NaF in rats. The rats were given an intraperitoneal dose of 26 mg NaF/kg, the approximate LD_{50} for animals weighing 200 to 300 g. At less than seven months-of-age both sexes seemed to be resistant to NaF toxicity, with the females less resistant than the males. At seven months or more, there were no differences between the sexes. These data are summarized in Table V-1.

These studies of acute fluoride toxicity are a representative sample of those available. They illustrate the essential characteristics. Other published studies of acute fluoride toxicity do not differ significantly in their content.

B. Chronic Toxicity

In practical terms, chronic effects of excessive exposure to fluoride have been most important in domestic animals, especially cattle (NAS 1971). For this reason the chronic toxicity of fluoride has been studied mainly in cattle and in sheep.

Table V-1 Effects of Age on Toxicity of Sodium Fluoride in Rats

Male Albino Rats				Female Albino Rats			
Age (months)	Av. Wt. (grams)	No. rats used	Mortality in 24 hr (%)	Age (months)	Av. Wt. (grams)	No. rats used	Mortality in 24 hr (%)
1	90	25	0	1	79	25	0
2	229	25	0	2	164	25	16
3	288	25	8	3	174	25	4
4	297	25	12	4	190	25	28
7	361	25	84	7	213	25	80
12	336	25	92	12	219	25	92

[a] Dose, 26 mg NaF/kg; Concentration, 20 mg/mL Water. No mortality was produced at a dose of 20 mg NaF/kg in comparable animals.

Adapted from Maynard et al. (1951).

The studies discussed in this section are a representative sample of those available. The conclusions from the studies selected are consistent with those not discussed herein. The material presented was selected for the quality of the research effort that generated it and for its illustration of the essential characteristics of fluoride toxicity.

1. Bone

Suttie et al. (1961) exposed Holstein calves to dietary NaF. At the start of the experiment the calves were 6- to 27-weeks-old. Sodium fluoride was added to their diet to supply 1.0, 1.2, 1.4, 1.6 and 2.0 mg fluoride/kg/day. The majority of the cattle were removed from the experiment either during or at the end of the second lactation period. Length of exposure in calendar time was not specified and varied from animal to animal. Severe fluorosis (characterized by rapid weight loss, general deterioration of condition, intermittent lameness and stiffness) was consistently associated with a skeletal fluoride concentration greater than 5,500 ppm. This concentration was reached by the first lactation in cows receiving 2.0 mg fluoride/kg/day and by the second lactation in cows receiving 1.6 mg fluoride/kg/day. The authors stated that a fluoride level in bone in excess of 5,500 ppm is one of the most reliable indices of fluoride toxicosis.

Shupe et al. (1963) studied the effects of dietary fluoride on 32 Holstein-Friesian dairy heifers. The animals received 12 (normal), 27, 49 or 93 ppm fluoride (equivalent to 0.30, 0.64, 1.17 and 2.08 mg/kg/day) on a total dry matter basis in their diet from age three to four months until 7.5 years. Eight animals were used in each of the four dose groups. Changes in bone were marked at 93 ppm (2.08 mg/kg/day), moderate at 49 ppm (1.17 mg/kg/day) and very slight at 27 ppm (0.64 mg/kg/day). There were no discernible effects on bone at the 12 ppm level (0.30 mg/kg/day). These data are summarized in Table V-2.

Affected bones appeared chalky white and had roughened, irregular periosteal surfaces. They were also larger and heavier than normal. Puffy joints and intermittent lameness developed in some cows in which osteofluorotic lesions were palpable. Shupe et al. (1963) considered lameness and stiffness to be inconclusive measures of fluoride toxicity. Bone lesions were scored according to the scheme in the legend of Table V-2.

Fluoride concentrations in dry, fat-free rib biopsy samples increased with increasing time of exposure for all dose groups. After 7.3 years (2,663 days) the fluoride concentration was approximately 900 ppm in animals on the normal diet. At this same time, the rib fluoride concentrations were approximately 2,500, 5,500 and 8,200 for the cattle receiving 27, 49 and 93 ppm fluoride in the ration, respectively. The rate of increase with time was greatest in those cattle administered 93 ppm fluoride. The first clinically discernable bone lesions appeared on the medial surface of the proximal third of the metatarsal bones and were bilateral. These effects were observed after 1.5 to 2 years in cattle on the 93 ppm fluoride ration and after 3.5 to 4 years in cattle on the 49 ppm fluoride ration. As the degree of osteofluorosis

Table V-2 Effects of Ingested Fluoride on Dairy Cattle Fed Various Levels of Sodium Fluoride From 4 Months to 7.5 Years of Age[a]

				Chronic fluorosis		
Average	Age (years)	Normal conditions	No adverse effects	Borderline	Moderate	Severe
F in moisture-free diet (ppm)	2	Up to 15	15-30	30-40	40-60	60-109
	4	Up to 15	15-30	30-40	40-60	60-109
	6	Up to 15	15-30	30-40	40-60	60-109
Teeth classification[b] (incisors)	2	0-1	0-2	2-3	3-4	4-5
	4	0-1	0-2	2-3	3-4	4-5
	6	0-1	0-2	2-3	3-4	4-5
Teeth classification[b] (molars)	2	0-1	0-1	0-1	0-1	0-3
	4	0-1	0-1	0-1	1-2	1-4
	6	0-1	0-1	1-2	1-3	1-5
F in bone (ppm)	2	401-714	714-1,605	1,605-2,130	2,130-3,027	3,027-4,206
	4	706-1,138	1,138-2,379	2,379-3,138	3,138-4,504	4,504-6,620
	6	653-1,221	1,221-2,794	2,794-3,788	3,788-5,622	5,622-8,676
F in urine (ppm)	2	2.27-3.78	3.78-8.04	8.04-10.54	10.54-14.71	14.71-19.86
	4	3.54-5.3	5.3-10.32	10.32-13.31	13.31-18.49	18.49-25.63
	6	3.51-6.03	6.03-11.29	11.29-14.78	14.78-20.96	20.96-30.09
F in milk (ppm)	2	Up to 0.12	Up to 0.12	0.08-0.15	0.15-0.25	0.15 and above
	4	Up to 0.12	Up to 0.12	0.08-0.15	0.15-0.25	0.15 and above
	6	Up to 0.12	Up to 0.12	0.08-0.15	0.15-0.25	0.15 and above
F in blood (ppm)	2	Up to 0.30	Up to 0.30	0.15-0.40	0.30-0.50	0.50 and above
	4	Up to 0.30	Up to 0.30	0.15-0.40	0.30-0.50	0.50 and above
	6	Up to 0.30	Up to 0.30	0.15-0.40	0.30-0.50	0.50 and above
Average F in soft tissues (ppm)	2	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20
	4	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20
	6	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20	Up to 1.20
Periosteal hyperostosis[c]	2	0	0-1	0-1	0-2	0-3
	4	0	0-1	0-1	0-3	0-4
	6	0	0-1	0-2	0-4	0-5
Secondary changes may occur[d]	All	Absent	Absent	Occasionally noticed	Present	Present

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[a] Data are based on controlled experiments, but also can be correlated with numerous field cases that have been extensively studied and evaluated.

[b] Incisors (average classification of erupted permanent teeth degree of fluoride effects): 0-normal, 1-questionable, 2-slight, 3-moderate, 4-marked, 5-excessive. Molars (average classification degree of wear): 0-normal, 1-questionable, 2-slight, 3-moderate, 4-marked, 5-excessive.

[c] Periosteal hyperostosis: 0-normal, 1-questionable, 2-slight, 3-moderate, 4-marked, 5-excessive.

[d] Stiffness and lameness, loss of body weight, reduced feed intake, rough hair coat, unpliable skin, and reduced milk production.

Adapted from Shupe et al. (1963).

increased, palpable hyperostoses appeared in the rami of the mandibular bones, and the 7th through 12th ribs became wider and thicker. The degrees of periosteal hyperostosis were classified as 0 = normal, 1 = questionable, 2 = slight, 3 = moderate, 4 = marked and 5 = excessive. Cattle on the normal diet were scored as normal through 6 years of age. Those cattle on 27 ppm ration were scored 0 to 1 through 6 years; those on 49 ppm ration were scored 0 to 2 at 2 years, 0 to 3 at 4 years, and 0 to 4 at 6 years; and those on 93 ppm ration were scored 0 to 3, 0 to 4 and 0 to 5 at 2, 4 and 6 years, respectively. Radiographs taken at age 7.5 years (approximately 7 years on fluoride) showed increased coarsening and thickening of the trabecular pattern with a ground glass appearance for cattle on the rations containing 49 and 93 ppm fluoride. Periosteal hyperostosis, subperiosteal increased density in some cases, endosteal and cortical porosity, and mineralized spurs at points of attachment of tendons to leg bones were also observed at these dose levels.

In the study of Shupe et al. (1963), no effects at any exposure level on hoofs, soft tissues or blood were found. Milk production was only affected after clinical signs of skeletal fluorosis, lameness and molar abrasion had developed. These observations imply the animals were not able, because of their advanced skeletal and dental fluorosis, to maintain a nutritional level adequate for milk production. Effects on milk production were found in the cows exposed to 49 and 93 ppm (1.17 and 2.08 mg/kg/day) fluoride. Suttie et al. (1957b) also found that the effects of fluoride on milk production were secondary to other clinical signs resulting in curtailed feed intake.

2. Teeth

Suttie et al. (1957a) added NaF to the ration of 24 Holstein heifers divided into six groups of four each. The animals were approximately two-years-old at the start of the experiment and exposure to fluoride was maintained for 5.5 years. Fluoride was mixed with the diet so that the cattle received 20, 30, 40 or 50 ppm added fluoride per day on the basis of dry feed weight (four animals per dose). These concentrations were equivalent to 0.53, 0.86, 1.03 and 1.36 mg/kg/day, respectively. The earliest observable indication of excessive exposure to fluoride was a mottling of the growing teeth. Mottling was scored according to the scheme of Hobbs et al. (1954), as follows:

Classification	Description
1	Normal Tooth
2	Questionable Effect
3	Marginal Effect
4	Definite Effect
5	Severe Effects

The latter two ratings are characterized by varying degrees of hypoplasia of the enamel and tooth. Slight mottling and wear (scored 3, marginal) was observed on the fourth incisors of the animals ingesting 0.53 mg/kg/day. Animals ingesting 0.86 to 1.36 mg/kg/day had teeth which were scored 4 or 5. These data, reflecting the results following 5.5 years of fluoride exposure, are summarized in Table V-3.

Table V-3 The Effects of Fluoride Fed as NaF on Various Physiologic Responses in Heifers

Lot	F[a] Added	Av. Fecal F[a] (dry wt.)	Av. Calf Bone F[a] (dry fat free wt.)	Milk F (whole milk)	Av. Score of Incisors Pair 3	Av. Score of Incisors Pair 4	Av. No. of Services[b]
I	0	14	11	0.16	1	1	2.1
II	20	--	86	0.31 0.29	1	3	1.5
III	30	27	136	0.30 0.38	2	4	2.1
IV	40	30	104	--	4	5	2.3
V	50	37	140	0.27 0.44	4	5	2.2

[a] Values are expressed as ppm fluoride.
[b] Average number of services per cow per year required for conception.

Adapted from Suttie et al. (1957a).

Subsequent to the appearance of effects on dentition, a total of four animals, two in lot IV and two in lot V, developed symptoms of fluorosis. These symptoms and their sequence were:

1. A refusal of fluoride-supplemented foods.
2. Excessive weight loss.
3. Stiffness in the legs with resulting lameness.

These effects were sufficient to debilitate the animals within several weeks. Such symptoms of fluorosis were not seen in the groups exposed to 30 ppm fluoride or less.

In the study of Shupe et al. (1963), pairs of heifers (three- to four-months-old) received 12 (normal), 27, 49 or 93 ppm of fluoride (equivalent to 0.30, 0.64, 1.17, and 2.08 mg/kg/day) on a total dry matter basis in the ration. In addition, each ration was supplemented with one of two levels of a concentrate or one of two levels of a Ca-P mixture. The experiment, therefore, included 32 animals divided into pairs among 16 treatment groups. The experiment continued until the animals were 7.5 years-old.

Depending on the amount of fluoride ingested, affected teeth erupted with different degrees of mottling, staining, hypoplasia and hypocalcification. Dental fluorosis was scored according to the scale described in Table V-2, which is essentially the same as that of Hobbs et al. (1954) and the following tooth classifications were established:

(0) Normal: smooth, translucent, glossy white enamel; tooth normal shovel shape.

(1) Questionable effect: slight change, exact cause not determined; may have enamel flecks; cavities may be unilateral or bilateral but with the absence of mottling.

(2) Slight effect: slight mottling of enamel; may have slight staining but no wear; teeth normal shovel shape.

(3) moderate effect: definite mottling and staining of enamel; coarse mottling (large patches of chalky enamel); teeth may have slight signs of wear.

(4) Marked effect: definite mottling, staining and hypoplasia; may have pitting of enamel; definite wear of teeth; enamel may be a pale cream color.

(5) Excessive effect: definite erosion of enamel with excessive wear of teeth; staining and pitting of enamel may or may not be present.

In cattle consuming the highest dose of fluoride (i.e., 93 ppm in the ration) the incisors were classified as 4 to 5, beginning as early as 2 years of age. The molars were classified as 0 to 3 at 2 years-of-age, 1 to 4 at 4 years and 1 to 5 at 6 years. For cattle at the dose of 49 ppm, the incisors were scored as 3 to 4 beginning at 2 years. In these same animals, the molars were scored as 0 to 1 at 2 years, 1 to 2 at 4 years, and 1 to 3 at 6 years. In cattle administered 27 ppm fluoride, the incisors were scored as 0 to 2 through 6 years-of-age and the molars were scored as 0 to 1 through 6 years. Incisors and molars of cattle administered the normal ration (12 ppm fluoride) were scored 0 to 1 throughout the 6 years. Thus, the cattle administered the diet containing 27 ppm (0.64 mg/kg/day) fluoride nearly represents a no effect level (NOAEL).

The effects of water-borne fluoride on sheep have been studied by Peirce (1959). Mature ewes (total of 150) were divided into three groups: Group A (control) was given drinking water having 0.3 ppm fluoride; fluoride was added to the drinking water of groups B and C so that they were exposed to 10 and 20 ppm fluoride, respectively. These ewes were mated over a period of six weeks and all the offspring were weaned when the youngest lamb was three-months-old. At this point the mothers were removed from the experiment. The experiment was continued until the younger animals (group A, 21 wethers and 11 ewe lambs; group B, 17 wethers; group C, 20 wethers and 10 ewe lambs) were almost seven-years-old. During the course of the experiment the animals drank almost nothing in the winter months and up to 3 to 4 L/day in the summer. For the whole experiment, mean intakes of fluoride were 0.25 mg/kg/day for group B and 0.48 mg/kg/day for group C.

Weight gain was not significantly affected by treatment with fluoride at any point in the experiment. Wool production was reduced in the groups receiving added fluoride in their drinking water. Sheep in groups B and C showed characteristic signs of dental fluorosis. These included mottling of incisors and molars, selective abrasion of the molars and wear of various types and degrees of severity on the incisors. The degree of mottling and erosion was slight in the sheep of group B but was severe in those of group C. Only one animal in group C appeared to be unaffected. Selective abrasion of molars occurred in about 25% of the sheep in group B and in all but two of the sheep in group C. In addition, the abrasion was more severe in group C. The fluoride content of bones and teeth was significantly increased in animals in groups B and C. See Table V-4 for a summary of these data.

3. Reproduction

The effect of fluoride in drinking water on the reproductive efficiency of Afrikander heifers was studied by Van Rensburg and De Vos (1966). At the start of the experiment the heifers were from 2.5- to 2.75-years-old and were free from tuberculosis, brucellosis and coital diseases. The animals were divided into five groups of ten animals each and breeding was started nine months after the start of the experiment. During the first two seasons the animals were served naturally, while artificial insemination was used in the last two seasons. Defluorinated superphosphate was added to the drinking water of some experimental groups (see Table V-5) at the rate of 1 g phosphorus/gallon. This was done in order to test the hypothesis that phosphate might retard the action of fluorine.

Table V-5 summarizes the fluoride exposure data and the breeding records of these animals. Inspection of these data shows that cows receiving 5, 8 or 12 ppm fluoride in drinking water (estimated to equal 0.55, 0.88 and 1.32 mg/kg/day, respectively) suffered significant decreases in calving rates (Figure V-1). The authors state that in Afrikander heifers not exposed to excessive fluoride, reproductive efficiency normally increased during the

Table V-4 Fluoride Concentration in Bones and Teeth of Sheep Drinking Fluoride-Supplemented Water

		Metacarpus		Rib		Molars	
Experimental Group	Fluoride Content of Water (ppm)	Fluoride in Ash (%)	Fluoride in Bone[a] (%)	Fluoride in Ash (%)	Fluoride in Bone[a] (%)	Fluoride in Ash (%)	Fluoride in Teeth[a] (%)
A	0.3	0.12	0.08	0.15	0.10	0.11	0.08
B	10	0.35	0.25	0.41	0.26	0.26	0.21
C	20	0.40	0.29	0.46	0.30	0.34	0.27

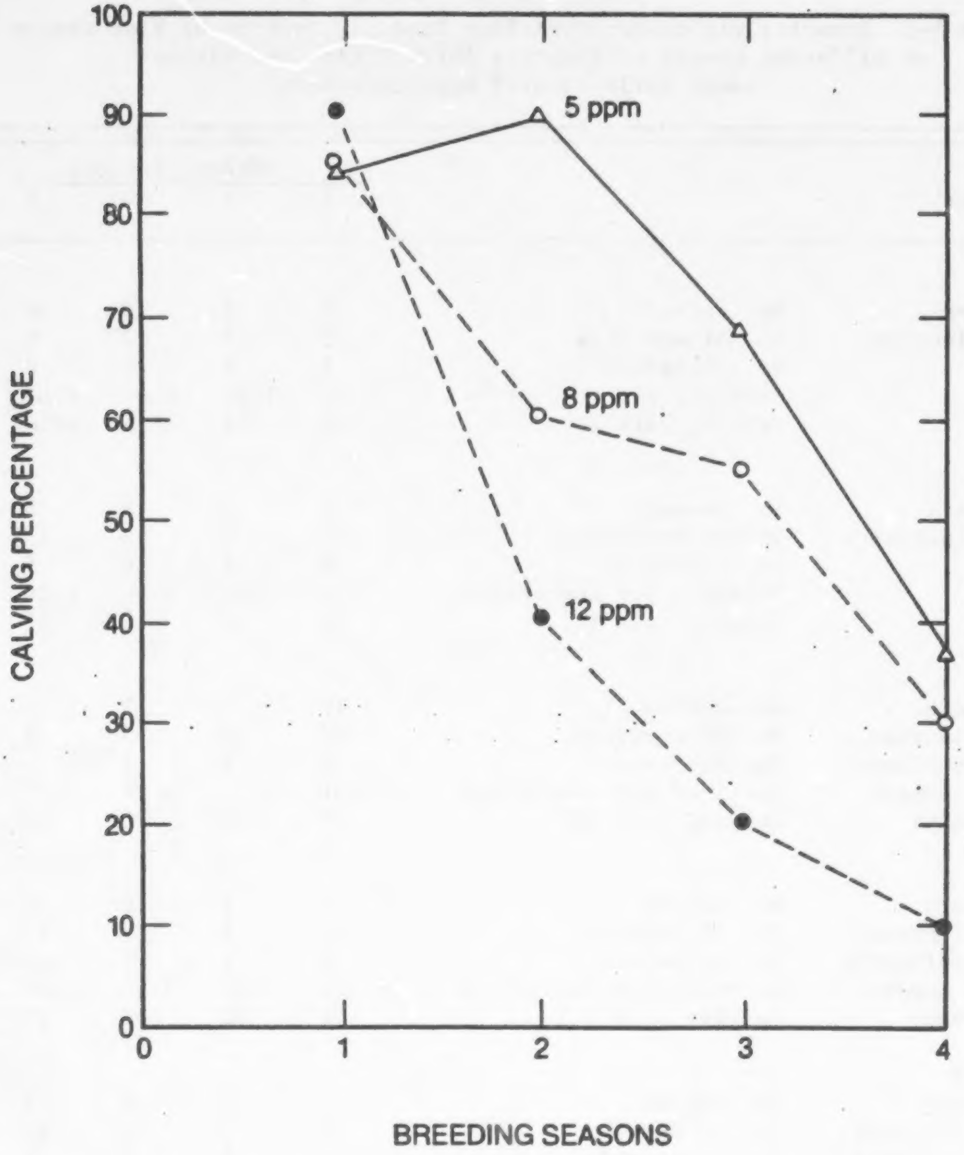
[a] Calculated on a dry, fat-free weight basis.

Adapted from Peirce (1959).

Table V-5 Breeding Efficiency Over Four Breeding Seasons of Five Groups on Different Levels of Fluorine Intake, With and Without Added Defluorinated Superphosphate

Group		Breeding Seasons			
		1	2	3	4
1					
9 Heifers	No. served	9	8	8	6
5 ppm fluorine	No. of services	9	8	12	8
	No. conceived	8	8	6	4
	Services per conception	1.12	1.00	2.00	2.00
	Calving rate (%)	88	88	66.7	44.4
2					
10 Heifers	No. served	10	6	9	8
8 ppm fluorine	No. of services	14	6	15	11
	No. conceived	8	6	6	5
	Services per conception	1.75	1.00	2.50	2.20
	Calving rate (%)	80	60	60	50
3					
10 Heifers	No. served	10	9	9	5
5 ppm fluorine,	No. of services	12	10	9	6
plus defluori-	No. conceived	8	9	7	3
nated super-	Services per conception	1.50	1.11	1.28	2.00
phosphate	Calving rate (%)	80	90	70	30
4					
10 Heifers	No. served	10	6	10	8
8 ppm fluorine,	No. of services	15	6	13	11
plus defluori-	No. conceived	9	6	5	1
nated super-	Services per conception	1.67	1.00	2.60	11.00
phosphate	Calving rate (%)	90	60	50	10
5					
10 Heifers	No. served	9	5	6	7
12 ppm fluorine,	No. of services	10	5	11	15
plus defluori-	No. conceived	9	4	2	1
nated super-	Services per conception	1.11	1.25	5.50	15.00
phosphate	Calving rate (%)	90	40	20	10
Total for 49	No. served	48	34	42	34
heifers	No. of services	60	35	60	51
	No. conceived	42	33	26	14
	Services per conception	1.43	1.06	2.31	3.64
	Calving rate (%)	85.7	67.3	53.1	28.4

Adapted from VanRensburg and DeVos (1966).



, Adapted from VanRensburg and DeVos (1966)

Figure V-1 Calving Rate of Cows on Three Levels of Fluoride Intake

period over which this study was conducted. The deleterious effects of exposure to excessive fluoride on reproductive performance preceded the development of clinical signs of fluorosis. This is significant as it suggests that the reproductive effects were not a consequence of ill health secondary to skeletal or dental fluorosis. However, by the end of the fourth breeding season, general ill health, loss of appetite, and erosion and mottling of teeth were increasingly evident.

Defluorinated superphosphate tended to exacerbate rather than mitigate the toxicity of waterborne fluoride (Table V-5). Van Rensburg and De Vos (1966) speculated that the defluorinating process may not have been completely effective and that the animals receiving defluorinated superphosphate may actually have been exposed to higher than indicated concentrations of fluoride. Therefore, the data for exposure groups 3, 4 and 5 should be interpreted with caution.

Suttie et al. (1957a) added NaF to the diet of Holstein heifers. The animals were two-years-old at the start of the experiment and exposure to fluoride was continued for 5.5 years. Fluoride was mixed in the ration so that the cattle received 0.53, 0.86, 1.06 and 1.36 mg added fluoride/kg/day. Over the course of this experiment there was no effect on reproduction as measured by the average number of services per conception. Other indices of reproduction were not evaluated in this study.

Hobbs and Merriman (1962) studied the effect of NaF on reproductive performance in Hereford heifers. These animals were free from tuberculosis and Bang's disease and were immunized against brucellosis. Sodium fluoride was added to feed so that over the nine-year period of exposure, groups of three calves received 0.17, 0.39, 0.59, 0.91, 1.03, 1.24, 1.56 and 1.96 mg fluoride/kg/day. The cows were yearlings at the start of the experiment. They were bred first when two-years-old, then at yearly intervals for nine years. The breeding records of these animals are summarized in Table V-6. It is apparent that there was some deficit in reproductive performance associated with exposure to 1.56 and 1.96 mg/kg/day. Exposure to less than 1.56 mg/kg/day did not have an obvious effect on reproductive performance.

The effect of fluoride exposure on reproductive performance in sheep was studied by Peirce (1959). He determined the percentages of lambs born by two generations of experimental ewes (for example, 10 ewes giving birth to 10 lambs would be 100%). The first generation was divided into three groups of approximately 50 ewes/group (group A, control; group B, 10 ppm or 0.25 mg/kg/day; group C, 20 ppm or 0.48 mg/kg/day). The percentages of ewes which produced lambs were 93%, 98% and 98%, respectively. The actual percentages of lambs born were 115%, 124% and 121%, respectively. The second generation ewes retained in the experiment (11 in group A and 10 in group C) were mated first at age 18 months and thereafter at yearly intervals for a total of six gestations. The relevant data are summarized in Table V-7. These data show that provision throughout gestation of drinking water containing 10 or 20 ppm fluoride had no adverse effect on reproduction in these sheep.

Table V-6 Reproductive Performance of Hereford Heifers Exposed to Dietary NaF for Nine Years

Dose of Fluoride (mg F/kg/day)	No. of Cows At Start of Experiment	No. of Cows At End Of Experiment	Total No. Calvings Over 9 Seasons	Number Calvings Expected If 1 Calving/Year/Cow	Actual % of Expected Calvings
0.17	3	3	17	27	63
0.39	3	3	18	27	67
0.59	3	1[a]	11	16	69
0.91	3	3	23	27	85
1.03	3	3	17	27	63
1.24	3	3	20	27	74
1.56	3	3	12	27	44
1.96	3	2[b]	6	22	27

[a] One animal died in first year of experiment; one animal sacrificed in seventh year of experiment.

[b] One animal sacrificed in fifth year of experiment.

Adapted from Hobbs and Merriman (1962).

Table V-7 Effect of Fluoride Exposure on Reproductive Performance of Sheep

	Group A[a]			Group C[b]		
Year	Ewes Mated	Ewes Lambed	Lambs Born	Ewes Mated	Ewes Lambed	Lambs Born
1952	11	10	11	10	8	9
1953	11	11	13	9	8	12
1954	11	10	14	9	9	13
1955	11	10	11	9	8	12
1956	10	10	11	9	9	16
1957	10	7	8	8	7	8
Total	64	58	68	54	49	70
Total as Percentage of ewes mated		91%	106%		91%	130%

[a] Control animals (0.3 ppm F in drinking water).
[b] Test animals (20 ppm F in drinking water).

Adapted from Peirce (1959)

4. Growth

Some species differences are evident in the effect of fluoride on growth. Growth is not affected in most species at 100 ppm fluoride in the diet (Hodge and Smith 1965). Cattle, however, appear to be more susceptible. Suttie et al. (1957a) reported that at 50 ppm added fluoride, attainment and maintenance of the adult body weight was slightly depressed in a study on Holstein heifers fed rations containing 0, 20, 30, 40 or 50 ppm fluoride. In the study of Shupe et al. (1963) (see Section V.B.1.), Holstein heifers were fed rations containing 12 to 93 ppm fluoride; according to the analysis of Stoddard et al. (1963), growth was not significantly affected at any of these levels. Hobbs and Merriman (1962) reported that, in a ten-year study, 10 to 100 ppm (estimated 0.17 to 19.6 mg/kg) fluoride as NaF in the ration had no adverse effect on the body weight of cattle, whereas 200, 300 or 600 ppm (estimated 3.92, 5.88 or 11.76 mg/kg, respectively) resulted in lower weight. Peirce (1959) reported that ingestion of drinking water containing 0.3 to 10 or 20 mg fluoride/L (estimated 0.08, 0.25 or 0.48 mg/kg/day, respectively) by sheep for approximately seven years did not significantly affect weight gain. Hobbs et al. (1954) reported that ewes given rations containing up to 100 ppm (estimated 2.4 mg/kg) fluoride as NaF over a three-year period showed no differences in final weight compared to control animals; weight gains were decreased at 200 ppm (estimated 4.8 mg/kg).

5. Kidney

Sufficiently high doses of fluoride have been shown to produce a vasopressin-resistant polyuria resembling nephrogenic diabetes insipidus (Rush and Willis 1982). Investigations into the mechanism of this effect have been the subject of several reports. Roman et al. (1977) found that rats (male, Fisher 344 strain, weighing 250 to 350 grams), after four daily subcutaneous injections of 7.6 mg fluoride/kg body weight (as NaF), showed statistically significant ($P<0.05$) increases in urinary flow, glomerular filtration rate, percent sodium excretion and percent water excretion. They suggested that fluoride inhibits tubular resorption by inhibiting active chloride transport in the ascending limb of the loop of Henle.

Rush and Willis (1982) have reported that fluoride inhibits sodium chloride absorption in the ascending limb of Henle's loop and antidiuretic hormone-mediated water absorption across the collecting duct. In this study, rats (male, Fisher 344 strain, weighing 200 to 250 grams) received intravenous infusions of 5.7, 27.9 or 41.8 µg fluoride/kg body weight/minute for 2.5 hours. Whitford and Taves (1971) reported that in 16 female rats (weighing approximately 200 g each, strain not mentioned) receiving 0.4 to 4 µg fluoride intravenously over a two-hour period, plasma fluoride concentrations of 950 µg/L were associated with a definite increase in the rate of urine flow. From the above studies and many others with similar results, it can be concluded that the acute effects of fluoride on the kidney are related to both the peak blood concentration of fluoride and the length of time the kidney is exposed to high concentrations.

Hodge and Smith (1965) reviewed a number of chronic studies of fluoride ingestion by various species, and concluded that histological and functional changes can be seen after single doses of 20 to 30 mg/kg and that renal injuries do not develop when the drinking water contains less than 100 ppm fluoride.

6. Cardiovascular System

Leone et al. (1956) investigated the effects on blood pressure and heart rate of fluoride administered intravenously to dogs. Blood pressure and heart rate were decreased at doses of 20 to 30 mg fluoride/kg, and respiratory rate was increased. At 31 mg/kg, atrioventricular nodal rhythm, ventricular tachycardia and ventricular fibrillation were evident. Caruso and Hodge (1965) reported that oral administration of 10 mg fluoride/kg in mongrel dogs (three males and nine females weighing 6.9 to 16.3 kg) did not evoke hypotension, 15 mg fluoride/kg decreased blood pressure in two of three dogs, and 23 or 36 mg fluoride consistently depressed blood pressure in three dogs. Caruso et al. (1970) summarized published observations on the effects of fluoride on blood pressure in dogs and concluded that orally, a dose of at least 9 mg fluoride/kg is required to bring about a hypotensive effect. Sodium fluoride intravenously increased respiratory rate in proportion to the decrease in blood pressure. Death was caused by respiratory arrest, the heart continuing to beat for a time after breathing stopped. Ventricular fibrillation occurred terminally. Strubelt et al. (1982), however, concluded from their studies with male Wistar rats (weighing 340 to 420 g) that cardiovascular failure resulting from cardiodepressive and vasodilating effects of fluoride, rather than respiratory depression, was the cause of death.

Effects on the electrophysiology and histology of the rabbit heart have been reported by Takamori (1955). In these experiments, rabbits (mature white rabbits weighing 2 kg, 37 treated and 16 controls, sex not specified) received daily oral doses of 4.5, 13.5, 22.5 or 45 mg fluoride/kg (as NaF). Duration of the study is not clear from the report, though electrocardiograms are shown for rabbits receiving 4.5, 13.5 or 22.5 mg fluoride/kg for 62, 20 or 59 days, respectively, and histological sections are shown for 4.5 mg/kg at 132 days, for 30 mg/kg at 19 and 51 days, and for 50 mg/kg at 31 and 60 days. The author indicated that electrocardiograms showed depressed ST, inverted T, prolonged QT inverval, multi-focal ventricular premature contraction, bundle branch block and pulmonary P. Histologically, the heart muscle showed regressive degeneration, infiltration of cells, hyperemia, hemorrhages and thickening of the vessel walls. The effects were stated to be proportional to the amount of fluoride fed and the duration of the feeding.

Complete histopathologic studies were done by Taylor et al. (1961) on surviving rats (albino, male, Rochester strain, 75-days-old, weighing 200 to 270 grams) sacrificed 30 days after receiving single injections of 3.6 to 21.7 mg fluoride (as NaF)/kg given intravenously or intraperitoneally. No effects were seen in the heart, thyroid, lung, salivary gland, stomach, intestine, liver, adrenal, testis or femur.

In a chronic study reported by Hansen (1978), mice (female, CSE mice, 3 to 4-weeks-old, initially weighing 22.5 to 25.5 grams) were given drinking water containing 1 to 6 mg fluoride (as NaF)/L for six months. No histological effects attributable to fluoride were seen in the heart, stomach, intestines or bones.

7. Thyroid

The fact that iodine is taken up by the thyroid gland has led to a concern that fluorine, another halogen, might also become concentrated in this organ. Studies with ^{18}F, however, have shown this not to be the case; concentrations do not exceed those found in the blood (Hein et al. 1956). The available evidence indicates that structural and/or functional alterations in animals are not produced at or below fluoride concentrations of 50 mg/L in drinking water (Hodge and Smith 1965, Harris and Hayes 1955).

C. Teratogenicity

No information on the teratogenicity of fluoride in animals was located in the published literature.

D. Mutagenicity

Mohamed and Chandler (1976) studied the clastogenic effects of fluoride added as NaF to the drinking water of highly inbred male mice. The mice weighed 20 to 25 grams at the start of the experiment. The treatment levels were 1, 5, 10, 50, 100 and 200 ppm fluoride (estimated to equal 0.2, 1.0, 2.0, 10, 20 and 40 mg/kg/day, respectively). A total of 12 groups of mice were used (72 mice in all). At each dose level, mice were exposed for either three weeks or six weeks. The authors reported that cytological studies on bone marrow cells and on spermatogenesis indicated the presence of fragments, bridges and other chromosomal abnormalities.

The *in vitro* effects of NaF on mouse, sheep and cow oocytes and the *in vivo* effects of NaF on mouse oocytes were studied by Jagiello and Lin (1974). For the *in vitro* experiments, oocytes were removed from donor animals and incubated under conditions which stimulated meiosis. Sodium fluoride was added in fetal calf serum to mouse oocytes at total concentrations from 0.01 to 0.4 mg NaF/mL, and in sheep serum to sheep and cow oocytes at total concentrations from 0.01 to 0.2 mg NaF/mL. Observed effects of NaF treatment included inhibition of division, atresia and fragmentation of chromosomes. Sheep and cow oocytes were more sensitive than mouse oocytes to these NaF treatments. For *in vivo* experiments, mice were treated parenterally with NaF. Oocytes were then harvested for the study of meiosis. Several dosing regimens were used:

A. 500 μg NaF/mouse, intravenous.
B. 500 μg NaF/mouse, subcutaneous.
C. 250 μg NaF/mouse/day for 16 days, subcutaneous.
D. 5 μg NaF/g body weight/day for 35 days, subcutaneous.

Meiotic abnormalities were seen in 6 of the 28 cells examined from regimen A. These were cells at metaphase II with fuzzy, indistinct borders, and one cell had an abnormal anaphase-I-telophase-I. None of the other regimens (B, C or D) resulted in the formation of abnormal oocytes.

In contrast to the results of Mohamed and Chandler (1976), Kram et al. (1978) found no effect of NaF in drinking water on the frequency of sister chromatid exchange in mice. Twelve-week-old mice were taken from colonies which had been maintained for at least the seven prior generations on a low-fluoride diet (estimated to equal less than 0.1 mg/kg/day) or a high-fluoride diet (50 ppm - estimated to equal 10 mg/kg/day). Sodium fluoride was added to the drinking water of the group exposed to 50 ppm fluoride. Sister chromatid exchange status was identified in a separate laboratory with no knowledge of the fluoride status of the animals. No significant differences in sister chromatid exchange status were found between the low- and high-fluoride groups.

Data consistent with those of Kram et al. (1978) were obtained by Martin et al. (1979). Mice were taken from a colony that had been maintained for at least five generations on a diet containing 0.5 ppm fluoride (estimated to equal 0.1 mg/kg/day) and drinking water having 0 to 50 ppm fluoride (estimated to equal 0 to 10 mg/kg/day) added as NaF. Testis and bone marrow cells from these mice were subjected to cytological analysis (number of breaks, fragments, deletions, multivalents and multiradicals). No deleterious effects of fluoride exposure on chromosomes from testis and bone marrow cells were found. See Table V-8, Experiment 1, for a summary of the data.

Table V-8 Bone Fluoride and Chromosomal Aberrations in Bone Marrow and Testis Cells in Mice Receiving Water with Different Fluoride Levels

	Bone Fluoride		Bone-Marrow Cells				Testis Cells			
					Aberrations				Aberrations	
Group	No. of Mice	g% in Ash	No. of Mice	Cells Scored	No. of Cells	Rate (%)[a]	No. of Mice	Cells Scored	No. of Cells	Rate (%)[a]
Experiment 1										
Lifetime										
0 ppm F	9	0.0019 ± 0.0001[b]	9	427	3	0.67 ± 0.33[b]	8	399	4	1.00 ± 0.65[b]
50 ppm F	6	0.86 ± 0.03	7	279	1	0.28 ± 0.28	7	350	2	0.57 ± 0.57
Experiment 2										
One week										
0 ppm F			8	400	13	3.25 ± 1.00	9	450	3	0.33 ± 0.17
Six weeks										
0 ppm F	5	0.011 ± 0.003	5	250	3	1.20 ± 0.49	5	154	1	0.40 ± 0.40
0 ppm F + TEM	4	0.008 ± 0.001	4	122	18	12.50 ± 3.68	5	240	10	4.00 ± 2.61
1 ppm F	10	0.011 ± 0.001	9	319	3	0.67 ± 0.47	10	336	5	1.0 ± 0.80
5 ppm F	10	0.021 ± 0.001	7	350	3	0.86 ± 0.59	10	424	2	0.40 ± 0.27
10 ppm F	10	0.036 ± 0.002	8	316	1	0.42 ± 0.42	10	428	12	2.7 ± 2.0[c]
50 ppm F	5	0.151 ± 0.009	5	250	1	0.40 ± 0.40	5	182	1	0.40 ± 0.40
100 ppm F	10	0.295 ± 0.019	8	333	3	0.75 ± 0.53	10	414	1	0.20 ± 0.20

[a] The aberration rate (% cells examined with aberrations) was calculated for each mouse and the average for the group and its standard error are given.

[b] These values represent the mean ± standard error of the mean.

[c] One of the 10 animals in this group contained 9 cells with aberrations among the 44 cells examined. When this animal was excluded, the aberration rate among the other 9 animals was 0.78 ± 0.57.

Adapted from Martin et al. (1979)

Martin et al. (1979) also maintained mice for six weeks on drinking water containing 1, 5, 10, 50 or 100 ppm fluoride (estimated to equal 0.2, 1.0, 2.0, 10 or 20 mg/kg/day) as NaF. These groups and their controls did not differ in average intake of food or fluid or in average weight gain during the course of fluoride exposure. At the end of the exposure period bone marrow and testis cells were examined for chromosomal aberrations. No significant differences between control and exposed groups were found in rates of bone marrow chromosomal aberrations (see Table V-8, Experiment 2). Some heterogeneity in chromosomal aberration rates in testis cells was found. This heterogeneity was attributable to one animal in the group exposed to 10 ppm fluoride. Statistical analysis of the data showed no significant effect of exposure to fluoride on the number of chromosomal abnormalities in testis cells (see Table V-8, Experiment 2).

The mutagenicity of NaF was tested in *Salmonella typhimurium* and in *Saccharomyces cerevisiae* by Martin et al. (1979) (see Table V-9). Sodium fluoride was added to plates at 0.1, 1, 10, 100 and 500 μg/plate, with and without microsomal enzyme preparations from rats treated with Aroclor 1254. There was no indication of mutagenic activity in this experiment. One test which gave an elevated result (TA100) was repeated. There was no repetition of the elevated result.

E. Carcinogenicity

No information on the carcinogenic potential of fluoride in animals was located in the literature. However, The National Cancer Institute initiated

Table V-9 Mutagenicity of Sodium Fluoride in Microbial Systems: Number of Responses Per Plate

Test Conditions	Salmonella typhimurium revertants/Plate							S. cerevisiae tryptophane + Convertants/Plate
	TA1535	TA1537	TA1538	TA98	TA100	TA100[a]	TA100[a]	D4
No activation								
Solvent control	18	21	11	24	132			23
Positive controls	<1000[b]	<1000[c]	<1000[d]	<1000[d]	795[b]			103[b]
Sodium fluoride (μg/plate)								
0.1	30	13	10	25	56			15
1.0	24	18	18	22	165			22
10.0	20	23	20	21	171			23
100.0	24	14	7	24	147			16
500.0	27	14	8	8	160			20
Activation[e]								
Solvent control	29	19	20	48	239	243	194	100
Positive controls	128[f]	>1000[g]	627[h]	>1000[h]	148[f]	748	>1000[f]	157[i]
Sodium fluoride (μg/plate)								
0.1	21	12	14	30	149		174	115
1.0	36	14	9	37	209		156	91
10.0	53	18	17	27	208		192	81
100.0	36	22	5	20	287		197	70
500.0	31	19	13	24	464	261	206	61
1000.0						259	158	
2000.0						289	202	

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[a] Repeat at high levels of NaF with activation.

[b] N-Methyl-N'-nitro-N-nitrosoguanidine, 10 g/plate.

[c] Quinacrine mustard, 10 g/plate.

[d] 2-Nitrofluorene, 100 g/plate.

[e] Equivalent concentration to 25 mg of wet tissue of a 9000 g supernatant fluid prepared from liver of Sprague-Dawley adult male rat induced by Aroclor-1254 five days prior to kill was added to each plate.

[f] 2-Anthramine, 100 μg/plate.

[g] 8-Aminoquinoline, 100 μg/plate.

[h] 2-Acet[illegible]minofluorene, 100 μg/plate.

[i] Dimeth[illegible]rosamine, 100 ;moles/plate.

Adapte[illegible]'artin et al. (1979).

studies, during August 1979, to determine the carcinogenic and/or toxicological potential of sodium fluoride (NaF) in rats and mice. The National Toxicology Program (NTP) took over the responsibility for oversight of the studies in November 1982. The studies consisted of three parts: (1) a one-month subchronic study; (2) a six-month subchronic study with dosages based on the previous experiment; and (3) a two-year chronic study based on data from the six-month subchronic experiment (maximum doses of NaF which were not expected to affect the longevity of mice and rats were used). The chronic study began in December 1981 and terminated in December 1983. Unfortunately, problems developed seven months into the chronic study. The problems were not treatment related (some rats in both the treatment and control groups exhibited toxicollis and ocular lesions), but may have been related to the diet which was low in several trace elements and vitamins. The validity of the study was questioned and a new chronic study was scheduled. The Technical Report from the new study should be issued in 1988.

F. Other

Other manifestations of chronic fluoride toxicity in various species have been reported in the literature, but have not been reviewed here because (1) they have been described in only one or, at best, a very few investigations, (2) the dosages of fluoride employed have been far beyond anything to be encountered in the use of fluoridated water supply or (3) there are uncertainties about study protocols. Examples of these "one of a kind" effects include production of urinary calculi and effects on collagen, plasma fibrinogen, hyperglycemia, adenyl cyclase activity, enzymes, adrenal function, renal stones, otosclerosis or mineral levels in different organs.

G. Summary

The intravenous LD_{50} of fluoride in dogs is approximately 20 mg/kg. Dogs survived oral doses of up to 3,100 mg NaF/kg. Age and sex influenced the acute lethality of NaF in rats. In these studies, young rats (seven-months-old or less) were less sensitive than older rats and young male rats were less sensitive than young females.

Chronic exposure of cattle to fluoride added to their ration caused symptoms of dental and skeletal fluorosis. Fluoride added to the ration at 27 ppm (approximately 0.64 mg/kg/day) on a dry weight basis was tolerated with only minor effect. Higher concentrations, 49 and 93 ppm (1.17 and 2.08 mg/kg/day, respectively) produced serious symptoms of dental and skeletal fluorosis. The appearance of dental fluorosis preceded that of skeletal fluorosis. Milk production was impaired only after lameness and loss of appetite were apparent. One study showed that heifers exposed to as little as 5 ppm fluoride in their drinking water suffered impaired reproductive performance, but other studies found no effect on heifer reproduction at dietary fluoride concentrations more than twice that amount. Sheep exposed chronically to 10 or 20 ppm fluoride in their drinking water developed significant dental fluorosis and produced less wool. Weight gain was not affected and there was no effect on reproductive performance.

Growth in most species is unaffected by dietary concentrations of fluoride of 100 ppm or less. Cattle appear to be more sensitive, and growth has been reported to be affected slightly at 50 ppm. However, one investigation found no adverse effects at 100 ppm.

The kidney responds to acutely toxic doses of fluoride by failure to properly resorb water, leading to polyuria. Renal injuries do not develop when drinking water contains less than 100 ppm fluoride.

In dogs, oral doses of 9 mg fluoride/kg have been reported to cause hypotension, electrocardiogram irregularities and slowing of the heart.

Structural and/or functional changes of the thyroid gland in animals are not produced at fluoride concentrations of 50 mg/L in the drinking water.

Sodium fluoride in drinking water was reported to be clastogenic for mice but this result could not be confirmed in at least two other studies. Sodium fluoride was not mutagenic in *Salmonella typhimurium* or in *Saccharomyces cerevisiae*. No information on the teratogenicity or carcinogenicity of fluoride in animals was found in the literature.

VI. HEALTH EFFECTS IN HUMANS

A. Beneficial Effects

1. Teeth

The principal beneficial effect attributed to fluoride is its role in prevention of dental caries. A detailed review of the literature in this area will not be attempted here because it has been adequately addressed elsewhere in this document. Studies have been reviewed that describe the continuum from beneficial effects to adverse dental fluorosis with increased exposure to fluoride. A summary of the daily fluoride intake levels considered to be protective against both dental caries and possibly osteoporosis is provided in Table VI-1. A recent study by Driscoll et al. (1983) demonstrated that an increase in the average drinking water fluoride concentration from 1.06 to 2.08 mg F/L resulted in significant ($P<0.05$) reduction of dental caries of school children (8- to 16-years-old) in several Illinois communities. The authors noted, however, that communities with higher drinking water concentrations (up to 3.84 mg F/L) did not result in any additional significant dental caries reduction at $P<0.05$ level. Further details of this study (which also evaluated the incidence of dental fluorosis) are discussed in Section VI.C.3.

Fluoride is also believed to improve the esthetic appearance of teeth. As part of the Newburgh-Kingston fluoride demonstration, A. L. Russell recorded the occurrence of developmental enamel hypoplasias (not related to fluoride in drinking water) in children 7- to 14-years-old (Ast et al. 1956).

Table VI-1 Food and Nutrition Board Estimated Adequate and Safe Intakes of Fluoride

Age Group	Estimated Weight (kg)	Recommended Intake of Fluoride (mg/day)	Estimated Equivalences (mg/kg/day)
<6 months	6	0.1-0.5	0.02-0.08
6-12 months	9	0.2-1.0	0.02-0.11
1-3 years	13	0.5-1.0	0.04-0.08
4-6 years	20	1.0-2.5	0.05-0.13
7 years-adulthood	30[a]	1.5-2.5	0.05-0.08
Adults	70	1.5-4.0	0.02-0.06

[a] Estimated weight for children seven to ten years old.

Adapted from NAS (1980).

In Kingston, where the drinking water contained 0.05 mg F/L, 115 (18.7 percent) of the 612 children examined showed these nonfluoride opacities. Only 36 (8.2 percent) of 438 children using the fluoridated Newburgh water (1.0 to 1.2 mg F/L) showed these changes. Ast et al. (1956) suggested that this fluoride drinking water concentration (1.0 to 1.2 mg F/L) appeared to reduce the incidence of hypoplastic spots on the teeth. Richards et al. (1967) have suggested that teeth classified as showing questionable, very mild or mild dental fluorosis are desirable from an esthetic point of view.

2. Bone

The therapeutic use of sodium fluoride as a means of inducing new bone growth in cases of osteoporosis is under active investigation. For example, Jowsey et al. (1972) described the effects in 11 patients with progressive osteoporosis who were administered 30, 45, 60 or 90 mg of NaF daily. In four of the patients the dose was increased from 30 to 60 mg daily and in another patient increased from 45 to 90 mg daily. In one instance the dose was decreased from 60 to 30 mg per day. The patients, 10 of whom were female, ranged from 54 to 72 years-of-age. All subjects received vitamin D twice weekly and a daily supplement of calcium. Treatment was continued for 12 to 17 months. Bone biopsy samples were taken before and after treatment and biochemical studies were also performed. The results indicate that administration of less than 45 mg of NaF daily does not consistently increase bone formation, but that 60 mg or more resulted in the production of abnormal bone. Side effects were evident in at least one patient receiving 30 mg NaF. Mild arthralgia and stiffness of the joints were reported by four patients and occasional epigastric dyspepsia was experienced by six patients. Daily addition of vitamin D and more than 600 mg Ca appeared to prevent increased bone resorption and even to decrease resorption. The authors concluded that doses of 50 mg of NaF daily, supplemented with 600 mg or more of calcium daily and 50,000 units of vitamin D twice weekly should increase skeletal mass without undersirable skeletal effects. Also, further vertebral fractures should cease after several years of treatment.

Dambacher et al. (1978) treated 33 post-menopausal women with 100 mg NaF daily for two years and another 23 similar patients with 50 mg NaF daily for two years. A decrease of cortical bone was evident at both dose levels. However, cancellous bone was increased to some extent in half of those receiving the lower dose, and in over 70 percent of those receiving the higher dose. The findings also suggested that two years of treatment at the lower dose or one year at the higher dose avoided new vertebral fractures. Gastrointestinal discomfort sometimes combined with nausea was encountered chiefly at the higher dose, but was of minor clinical importance. Osteoarticular pain was the major side effect of fluoride therapy and was seen in about 60 percent of the patients at both dose levels. The maximum effect was seen after 6 to 12 months of treatment and then gradually disappeared. In 18 percent of the patients treatment had to be discontinued.

More recently Riggs et al. (1982) reported findings with regard to the occurrence of vertebral fracture in post-menopausal osteoporosis. Five groups of women, totaling 165 patients, were studied during the period from 1968 to 1980. Treatment regimens included: (1) controls (placebo or no treatment),

(2) calcium supplement with or without vitamin D, (3) fluoride plus calcium with or without vitamin D, (4) estrogen and calcium with or without vitamin D and (5) fluoride, calcium and estrogen with or without vitamin D. Fluoride doses were 40 to 60 mg NaF daily with a total of 61 patients (of 165 total) receiving fluoride. Of these, 23 (38 percent) developed adverse reactions which caused five of them to withdraw from the study. Thirteen of the 23 patients had joint pain and swelling or painful plantar facial syndrome; nine patients had severe nausea and vomiting, peptic ulcer or blood-loss anemia and one patient had both rheumatic and gastrointestinal symptoms. These effects were not seen in the control patients or in those treated with calcium alone or with viamin D, or with calcium plus estrogen with or without vitamin D. Among these groups, vitamin D was discontinued or the dose reduced because of hypercalcemia or hypercalciuria. Thirteen percent of the 60 patients receiving estrogen required hysterectomy or uterine dilation and curettage, but none had endometrial carcinoma or vascular thrombotic events.

Among the patients treated with NaF, 60 percent showed radiographically demonstrable increases in vertebral bone mass. Patients with these changes showed about one-seventh the fracture rate of the other patients. The incidence of fractures per 1000 patient-years for patients treated with fluoride, calcium and estrogen (with or without vitamin D) was significantly less than in controls ($P<1 \times 10^{-6}$), and also was significantly less than in those treated with fluoride and calcium (with or without vitamin D) ($P<0.001$). Riggs et al. (1982) point out that because fluoride simulates bone growth and estrogen inhibits its resorption, the effect of the two together would be expected to be additive. However, because of the significant side effects of estrogen (i.e., menometrorrhagia and induction of endometrial carcinoma), its inclusion in a combined therapy may not be warranted. The authors believe vitamin D should not be included because of the increased incidence of hypercalcemia or hypercalciuria or both.

Berstein et al. (1966) compared the incidence of osteoporosis, reduced bone density and collapsed vertebrae in two populations using water supplies with different concentrations of fluoride. In this study, a roentgenogram of the lateral lumbar area of the spine and answers to a questionnaire were obtained for 166 males and for 134 females who were long-term residents of areas where the water supplies contained to 4 to 5.8 mg F/L. Similar information was obtained for 312 male and 403 female long-term users of water supplies containing 0.15 to 0.3 mg F/L. More than 50 percent of the participants in each area had never lived outside their respective areas. The subjects of each sex in each population were grouped by age into those 45- to 54-years-old, 55- to 64-years-old and 65-years-old and over. Evidence of osteoporosis, reduced bone density and incidence of collapsed vertebrae were higher in the low fluoride area in both sexes. For women 55- to 64-years-old and 65-years-old and older the difference in prevalence of reduced bone density was significant at the $P<0.01$ level. In men the difference was significant only for the 55- to 64-year-old group ($P<0.05$). More subjects in the high fluoride area had normal or increased bone density. There was no significant difference in the incidence of collapsed vertebrae among male residents of the two areas. For women, the greater incidence of collapsed vertebrae in the low fluoride area was significant at the $P<0.05$ and $P<0.01$ levels for the 55- to 64-year-old and the 65-year-old and over groups, respectively. The authors concluded that

4 to 5.8 mg F/L in drinking water "materially and significantly" reduced the prevalence of osteoporosis and collapsed vertebrae, and that the effects were more pronounced in women than in men.

Using data from the 1973 to 1977 National Health Interview Surveys, Madans et al. (1983) compared the incidence of hip fractures as a measure of osteoporosis in two populations whose water supplies contained different concentrations of fluoride. More than 80 percent of 30,473 females plus 25,997 males used water containing less than 0.7 mg F/L. At least 80 percent of 21,810 females plus 18,034 males used water with more than 0.7 mg F/L. The hip fracture hospitalization rate for females in the low and high fluoride areas were 2.4 per 1000 and 2.2 per 1000, respectively. For males the rates were 1.0 and 1.1, respectively. The data suggest that a concentration of 0.7 mg F/L is not sufficient to protect against osteoporotic hip fracture. It was possible to identify 1,242 women and 1,111 men, 40 years of age or over, who used water supplies containing more than 0.7 mg F/L (specific concentrations could not be identified). Among these persons there was one case of hip fracture in the males and none in the females. The authors suggested that the hypothesis of a protective effect of higher levels of fluoride among women should not be ignored and that the optimal level exceeds 0.7 mg F/L.

3. Cardiovascular

In the study by Bernstein et al. (1966) the incidence of aortic calcification (as seen in the X-ray films) was less in residents of the high fluoride area than in those using low fluoride water. The difference was approximately 40 percent and was statistically significant for men in all age groups. Women in the 55- to 64-year-old group also showed a statistically significant difference in the incidence of aortic calcification. A similar trend, although not statistically significant, was observed in females 65-years-old and older.

4. Hearing

Shambaugh and Causse (1974) treated more than 4,000 patients with active otospongiosis of the cochlear capsule with sodium fluoride for 1 to 8 years, using doses of 40 to 60 mg daily with calcium and vitamin D supplements. The fluoride was administered in enteric coated tablets. In about 80 percent of the patients so treated there was a stabilization of the sensorineural component of hearing loss, with recalcification and inactivation of the actively expanding demineralized focus of otospongiosis. In a few cases hearing was improved, while in others the hearing loss continued to worsen. In a number of instances, cessation of therapy after stabilization of hearing and recalcification had been achieved was followed (two to seven years later) by reappearance of a demineralized focus and an increase in the sensorineural loss. Shambaugh and Causse (1974) recommend a maintenance dose of 20 mg daily of sodium fluoride after stabilization has been achieved.

Causse et al. (1980) gathered more evidence for the beneficial effect of fluoride therapy on otospongiotic foci through polytomographic studies, statistical analysis of 10,441 cases (with a follow-up of three months to ten years) and by comparing trypsin concentration in the perilymph before and after NaF therapy. Trypsin, which is toxic to hair cells and destroys collagen fibrils in the bony otic capsule, was significantly (no P value given) reduced in 66% of cases at moderate NaF (45 mg/day) doses. Fluoride therapy causes expulsion of cytotoxic enzymes into labyrinthine fluids and retardation of sensorineural deterioration. The long-term effect of therapy is the reduction of the bone remodelling activity of the otospongiotic focus. NaF therapy (in patients with cochlear deterioration and progressive cochlear component) can improve hearing in children but can only arrest deterioration in older patients. NaF may retard, but cannot release, stapedial fixation. Fluoride action reduces vertigo as an effect on vestibular function. Dosages used by the authors range from 3 to 60 mg/day depending on the nature of the otospongiotic impairment (in children only 1.5 to 10 mg/day are prescribed to avoid stunting growth). The authors observed no fluorosis in more than 10,000 cases.

5. Other

Black et al. (1949) examined the toxicity of sodium fluoride in relation to the beneficial effects of fluoride therapy in the treatment of malignant neoplasia. They described the effects of fluoride administered to more than 70 patients for periods of 5 to 6 months. Most of these subjects, suffering from malignant neoplastic disease, were being treated with metabolic inhibitors. Some were leukemic children 3- to 6.5-years-old, while others were adults including elderly individuals. Doses for the children were 20 to 50 mg NaF (9.0 to 22.5 mg F) four times daily. Doses for adults were 80 mg

NaF (36.3 mg F) four times daily. The material was administered orally with an antacid containing 4 percent aluminum oxide or as an enteric coated tablet to avoid gastric irritation. No evidence of systemic toxicity or of parenchymatous damage was seen which could be attributed to fluoride, even though some patients had received more than 27 g of sodium fluoride over a period of 3 months. Criteria evaluated included growth and development in the children, mottled enamel, eruption of permanent teeth, hematopoisis, liver function, albumin-globulin ratio, blood sugar and cholesterol concentrations and kidney function. Postmortem data from 4 cases showed no parenchymatous degeneration attributable to fluoride. In hypertensive patients a tendency was noted for decreased diastolic and systolic blood pressure. In two patients with functioning colostomies there was no apparent effect of the fluoride on the exposed mucosa of the colon.

In certain instances, Black et al. (1949) administered fluoride by intravenous infusion or injection. For example, a 16-year-old female with an adrenal carcinoma received a total dose of 5600 mg of sodium fluoride (2,533 mg F) in a period of nine consecutive days. There were no signs of acute or chronic toxicity. The injection of 400 mg of NaF (180 mg F) was painful in two of three instances, as was the injection of 800 mg of NaF (360 mg F). However, when infused, this amount was not painful.

B. Acute Toxicity

Lidbeck et al. (1943) described a mass poisoning in which 17 pounds of roach powder containing NaF was inadvertently added to a ten-gallon mixture of scrambled eggs. Two hundred and sixty-three cases of acute poisoning resulted and 47 of these were fatal. The episode is described by the authors as follows:

> The food was rejected by many of the patients because of a salty or soapy taste, while others complained of numbness of the mouth. Extremely severe nausea, vomiting and diarrhea occurred abruptly and at times simultaneously, and blood was noted in the vomitus and the stools in many instances. Soon after the meal there were complaints of abdominal burning and cramplike pains. General collapse developed in most instances but at variable periods of time, apparently depending on the concentration of the poison. This was characterized by pallor, weakness, absent or thready pulse, shallow unlabored respiration, weak heart tones, wet cold skin, cyanosis and equally dilated pupils. When this picture was pronounced, death almost invariably occurred. Local or generalized urticaria occurred in some instances, while in others there was a thick mucoid discharge from the mouth and nose. When death was delayed, and in some cases in which recovery occurred, there were paralysis of the muscles of deglutition, carpopedal spasm and spasm of the extremities. Convulsions and abdominal tenderness and rigidity were absent. In the majority of cases, death occurred between two and four hours after ingestion of the food, although in a few instances death was delayed for eighteen to twenty hours.

Hodge and Smith (1965) tabulated numerous reports of accidental and intentional poisonings with fluoride and concluded that a dose range of 5 to 10 grams of NaF can be cited as a reasonable estimate of a "certainly lethal [single] dose" for a 70-kg man. They noted that this corresponds to 70 to 140 mg/kg.

C. Chronic Toxicity

Prolonged exposure to excessive fluoride is known to cause skeletal and dental fluorosis. These effects will be described in detail, however, this section will first address occasional reports which have appeared in the literature suggesting a wide variety of toxic effects of fluoride exposure. These include abnormal sensitivity to fluoride (Grimbergen 1974, Waldbott 1962), mongolism (Rapaport 1959), a decreased margin-of-safety in people with renal insufficiency (Hanhijarvi et al. 1972, Juncos and Donadio 1972) and cancer (Yiamouyiannis and Burk 1977). The reports on mongolism and cancer will be discussed in Sections VI. D. and VI. F., respectively.

1. Sensitivity to Fluoride

Allergic or idiosyncratic sensitivity to fluoride has been the subject of a number of reports (Grimbergen 1974, Waldbott 1962, for others see NAS 1977). These studies contained various weaknesses in experimental design and in statistical analysis which have been discussed in a report by the NAS Safe Drinking Water Committee (NAS 1977). Waldbott presented case reports of people who were allegedly sensitive to fluoride. The NAS notes that this report has been criticized because Waldbott was, for some time, the only investigator to have reported this type of sensitivity. The study by Grimbergen (1974) appears to support the interpretation by Waldbott. Grimbergen administered either NaF in water or a placebo in a double-blind test to subjects who were suspected of being sensitive to fluoride. However, the statistical analysis of these data has been questioned by the NAS. They note that when a large number of samples are taken, some positive responses would be expected by chance. Grimbergen did not address this issue. Doubt that true sensitivity to fluoride exists has also been expressed by the World

Health Organization (WHO 1970). They reason that billions of people worldwide are regularly exposed to fluoride through tea drinking (brewed tea having more fluoride than the water from which it is made) or water fluoridation, so any subpopulation that is sensitive to fluoride should be readily apparent.

2. Bone

A number of factors govern the amount of fluoride in the skeleton. Important among these are (1) previous exposure, especially to a relatively constant fluoride intake; (2) the dose, which is reflected in the blood concentration; (3) renal status, which also affects the blood concentration, and (4) the age of the individual (Hodge and Smith 1981).

Endemic skeletal fluorosis is recognized in several parts of the world; it was first described in India (Shortt et al. 1937a). The most severe forms of generalized osteosclerosis also have been reported from this country. The findings in a 45-year-old Indian farmer suffering from fluorosis have been described in detail by Singh et al. (1962, 1963) and by Singh and Jolly (1970). Presumably, the individual lived all of his life in an area of the Punjab where the water supply contained 9.5 ppm fluoride. In this patient the bony contours showed irregular outgrowths. Sites of insertion of muscles and tendons showed excessive periosteal reaction and multiple exostoses. Irregular bone also was laid down in the joint capsules and interosseous membranes. The bones were much heavier than normal. The most pronounced changes were seen in the vertebral column; vertebrae were enlarged and showed marked lipping, and some were fused together. Bone ash from this subject contained 6,300 mg fluoride/kg of ash (6,300 ppm). The mechanical properties of the left radius and ulna of this subject were tested by Evans and Wood (1976). Their results showed that tensile strength, strain, energy adsorbed to failure and modulus of activity were reduced; compressive strength, strain and energy were increased. Compressive properties exceeded tensile properties; bone density was increased.

It should be recognized that the severe changes reported in areas of severe fluorosis such as the Punjab are not necessarily seen in all residents. Factors affecting the incidence of skeletal fluorosis include duration and level of exposure to fluoride in the environment, nutritional status, concurrent infections and physical severity of the individual's occupation (Singh and Jolly 1970).

Roholm (1937) identified three stages in the progression of skeletal fluorosis. These are (as quoted in Smith and Hodge 1979):

Phase I: osteosclerosis in pelvis and vertebral column. Coarse and blurred trabeculae, diffuse increased bone density to X-ray.

Phase II: increased density and blurring of contours of pelvis, vertebral column extended to ribs, extremities.

Phase III: greatly increased density of bone; irregular and blurred contours. All bones affected, particularly cancellous bones. Extremities thickened. Considerable calcification of ligaments of neck and vertebral column.

In addition, Fritz (1958) recommended adding two earlier stages of fluoride-induced changes, the earliest labeled "subtle signs," the second "phase 0-I." Both are characterized by slight radiological changes, e.g., enlargement of trabeculae in the lumbar spine. Both of these classification schemes have been developed from experience with industrial exposure to fluorides. Singh and Jolly (1970) point out that Roholm's Phase I is hardly ever seen in endemic fluorosis cases; most of these show the changes of phases II and III.

Franke et al. (1975) and Schlegel (1974) have attempted to correlate the concentration of fluoride in bone ash with the various osteosclerotic phases, as shown in Table VI-2. These data indicate that the early detection of slight radiological changes, e.g., enlargement of trabeculae in the lumbar spine, will be associated with bone ash fluoride concentrations of 3,500-4,500 ppm.

There is limited evidence to permit an estimate of the waterborne fluoride concentration associated with the appearance of fluoride osteosclerosis. For example, Hodge and Smith (1970) quote evidence that in the aluminum industry, average urinary excretions of 5 mg F/L in randomly collected samples are not associated with osteosclerosis. Dinman et al. (1976) indicated that aluminum workers whose average pre-shift urinary fluoride concentration is less than 4 mg F/L do not show radiographically demonstrable increases in bone density, altered trabecular patterns or ligamentous calcification. According to Figure III-3 (see Section III for greater detail), these urinary fluoride concentrations correspond to

Table V1-2 Correlation of Osteosclerotic Phases and Fluoride in Bone Ash

Osteosclerotic Phase	Mg Fluoride/kg Bone Ash (ppm)	
	Franke et al. (1975)	Schlegel (1974)
Normal	500-1,000	-
Fritz		
Prestage	3,500-4,500	-
O-I	5,000-5,500	6,900
Roholm		
I	6,000-7,000	5,200
II	7,500-9,000	7,500
III	>10,000	8,400

Adapted from Smith and Hodge (1979).

waterborne fluoride concentrations of approximately 5 and 4 mg F/L, respectively. Smith and Hodge (1959) have suggested that, in the human, osteosclerosis probably will not be seen with skeletal fluoride concentrations of 4,000 ppm (dry fat-free basis). They also state that effects will be observed in a small proportion of individuals with skeletal fluoride concentrations of approximately 6,000 ppm. These skeletal concentrations correspond to fluoride concentrations in the water of 4 and 6 mg F/L, respectively (Smith and Hodge 1959, Hodge and Smith 1981). It should be pointed out that at least at levels of intake corresponding to ≤ 0.1 ppm fluoride in the water, skeletal fluoride concentrations may vary up to ±50% (Smith 1983b).

3. Teeth

The tendency for excessive exposure to fluoride for prolonged periods during the time of tooth formation to cause fluorosis of dental enamel is of concern. Although the causative agent was not known at the time, a report of dental fluorosis (then called "mottled enamel") appeared in 1901 - Denti di Chiaie (Eager 1901). This report described the condition in certain Italian immigrants. Black and McKay (1916) and Kempf and McKay (1930) reported the same condition was endemic in parts of the U.S. Experimental data suggesting the connection between exposure to excessive amounts of fluoride and abnormalities in teeth appeared in 1925. McCollum et al. (1925) noted effects of dietary fluorine on the teeth of white rats and similar findings were reported by Schultz and Lamb (1925). The connection between fluoride and mottled enamel was first recognized by Smith et al. (1931).

Dean (1933) reported on the distribution of mottled enamel in the U.S., and in 1934 he published a classification system for mottled enamel (Dean 1934). This classification system is provided in Table VI-3.

Subsequently, Dean published a revised classification system for dental fluorosis (Dean 1942) which is still in use today. This system comprises six classifications into which the individual child or tooth may be assigned. Classification of an individual child is based on the two teeth in the child's mouth that show the most advanced forms of fluorosis. Since the classification of the severity of dental fluorosis is critical to the regulation of fluoride in drinking water, Dean's revised system is given in Table VI-4.

Dean (1942) used this system as the basis for defining a Community Fluorosis Index (CFI). The CFI is a means of comparing one group or population with another on the basis of average severity of fluorosis. It is computed by averaging the numerical fluorosis scores assigned to individual children within a given population.

Dean and Elvove (1935) defined the permissible maximum level of fluoride in a domestic water supply (or minimum threshold for dental fluorosis) as the highest concentration of fluoride incapable of producing a definite degree of dental fluorosis in as much as 10% of the group examined. The group examined for purposes of defining the CFI should consist of at least 25 children, 9-years-old or older, who, since birth, have continually consumed the water under investigation (i.e., used the water for both drinking and cooking). The

Table VI-3 Dental Fluorosis Classification by H. T. Dean - 1934

Classification	Criteria
Normal	The enamel presents the usual translucent semivitriform type of structure. The surface is smooth and glossy and usually of a pale creamy white color. For purposes of classification, all persons showing hypoplasia other than mottling of enamel are included in this category.
Questionable	There are slight aberrations in the translucency of normal enamel, ranging from a few white flecks to occasional white spots, 1 to 2 mm in diameter.
Very mild	Small opaque paper white areas are scattered irregularly or streaked over the tooth surface. It is principally observed on the labial and buccal surfaces, and involves less than 25% of the tooth surfaces of the particular teeth affected. Small pitted white areas are frequently found on the summit of the cusps. No brown stain is present.
Mild	The white, opaque areas on the surfaces of the teeth involve at least half of the tooth surface. The surfaces of molars, bicuspids, and cuspids subject to attrition show thin white layers worn off and the bluish shades of underlying normal enamel. Faint brown stains are sometimes apparent, generally on the upper incisors.
Moderate	No change is observed in the form of the tooth, but generally all of the tooth surfaces are involved. Surfaces subject to attrition are definitely marked. Minute pitting is often present, generally on the labial and buccal surfaces. Brown stain is frequently a disfiguring complication. It must be remembered that the incidence of brown stain varies greatly in different endemic areas, and many cases of white opaque mottled enamel, without brown stain, are classified as "moderate".
Moderately Severe	Macroscopically, a greater depth of enamel appears to be involved. A smokey white appearance is often noted. Pitting is more frequent and generally observed on all the tooth surfaces. Brown stain, if present, is generally deeper in hue and involves more of the affected tooth surfaces.
Severe	The hypoplasia is so marked that the form of the teeth is at times affected. The pits are deeper and often confluent. Stains are widespread and range from chocolate brown to almost black in some cases.

Table VI-4 Dental Fluorosis Classification by H. T. Dean - 1942

Classification	Criteria
Normal (0)	The enamel represents the usual translucent semivitriform type of structure. The surface is smooth, glossy, and usually of a pale creamy white color.
Questionable (0.5)	The enamel discloses slight aberrations from the translucency of normal enamel, ranging from a few white flecks to occasional white spots. This classification is utilized in those instances where a definitive diagnosis of the mildest form of fluorosis is not warranted and a classification of "normal" is not justified.
Very Mild (1)	Small, opaque, paper white areas scattered irregularly over the tooth but not involving as much as 25 percent of the tooth surface. Frequently included in this classification are teeth showing no more than about 1-2 mm of white opacity at the tip of the summit of the cusps of the bicuspids or second molars.
Mild (2)	The white opaque areas in the enamel of the teeth are more extensive but do not involve as much as 50 percent of the tooth.
Moderate (3)	All enamel surfaces of the teeth are affected, and surfaces subject to attrition show wear. Brown stain is frequently a disfiguring feature.
Severe (4)	All enamel surfaces are affected and hypoplasia is so marked that the general form of the tooth may be affected. The major diagnostic sign of this classification is discrete or confluent pitting. Brown stains are widespread and teeth often present a corroded-like appearance.

authors determined the CFI for four communities: Colorado Springs, Colorado; Monmouth, Illinois; Galesburg, Illinois; and Pueblo, Colorado. The mean annual fluoride content of the municipal water supplies and corresponding CFI for these communities were: Colorado Springs, 2.5 ppm - "slight"; Monmouth, 1.7 ppm - "slight"; Galesburg, 1.8 ppm - "slight"; and Pueblo, 0.6 ppm - "negative".

Galagan and Lamson (1953) studied the relationship between fluoride concentration in municipal waters and the CFI for communities with differing mean annual temperatures. They found that Arizona communities with mean air temperatures of 70°F had "objectionable" fluorosis (CFI exceeding 0.6) at about 0.8 mg fluoride/L in their drinking water, while midwestern communities with mean air temperatures of 50°F did not suffer "objectionable" fluorosis until their drinking water contained about 1.7 mg fluoride/L (see Figure VI-1). Richards et al. (1967) established slightly different optimal values for fluoride, using only three temperature zones, that were generally in agreement with the earlier studies. The authors pointed out that fluorosis was not entirely absent at optimum fluoride concentrations in drinking water. Their goal was to establish the fluoride levels at which "objectionable" fluorosis was present; objectionable was defined as moderate and severe fluorosis. The results of this study are summarized in Table VI-5. It should be noted, however, that a recent study in Canada (EHD 1982) concluded that water consumption is independent of temperature. Thus, the Agency has concluded that there is insufficient data to quantitatively incorporate temperature in drinking water regulations.

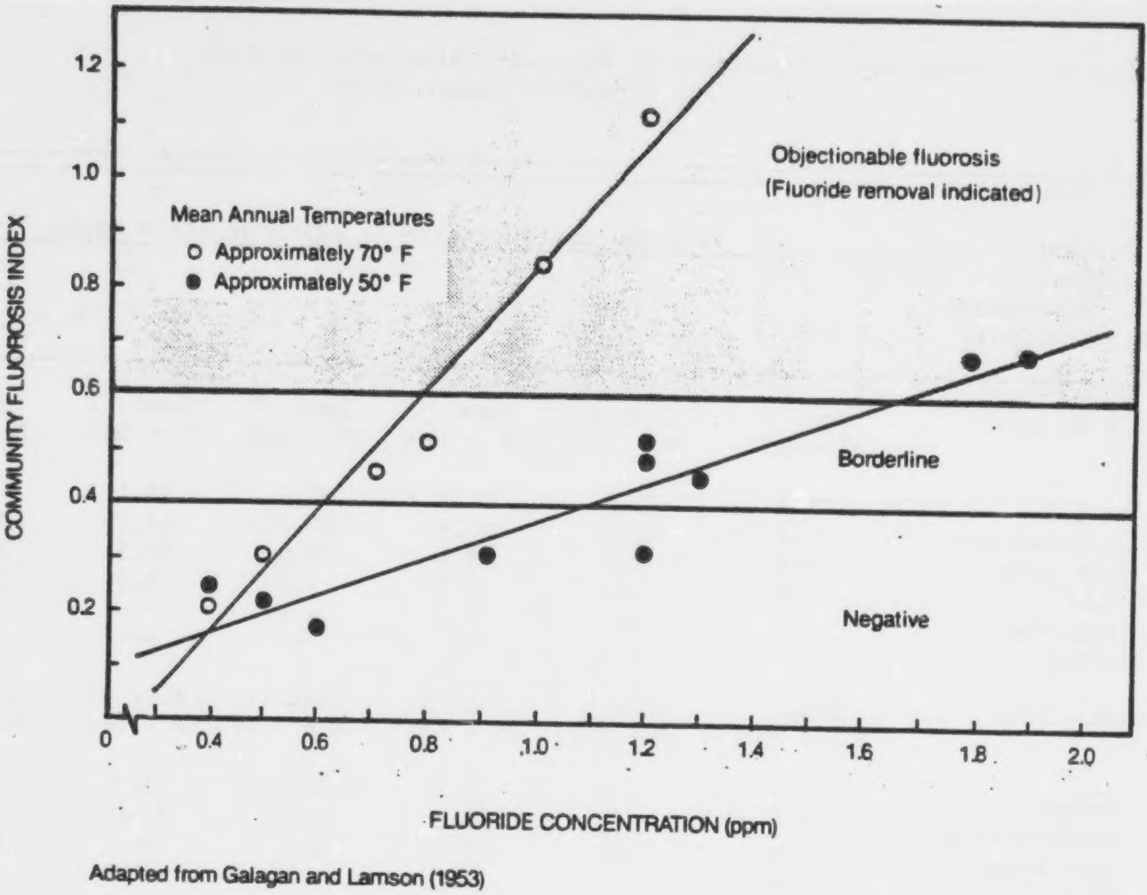

Figure VI-1 Relationship Between Fluoride Concentration of Municipal Waters and Fluorosis Index for Communities with Mean Annual Temperatures of Approximately 50° F (Midwest) and 70° F (Arizona).

Table VI-5 Percentage of Children by Fluorosis Diagnosis for Each Fluoride-Temperature Zone

Fluorosis diagnosis and temperature (Mean maximum)	Fluoride concentration in drinking water (ppm)					
	0.0-0.15	0.2 - 0.4	0.5 - 0.7	0.8 - 1.0	1.1 - 1.3	1.3 or more
65°F or lower	Zone 1 (N[a] = 330)	Zone 4 (N = 169)	Zone 7 (N = 340)	Zone 10 (N = 316)	Zone 13 (N = 302)	Zone 16 (N = 306)
Normal	97.3	71.6	44.7	40.0	33.1	11.1
Questionable	2.4	26.0	40.9	39.2	41.1	23.5
Very mild	0.3	2.4	13.5	18.0	22.5	29.5
Mild	---	---	0.9	2.8	3.3	15.7
Moderate	---	---	---	---	---	15.0
Severe	---	---	---	---	---	5.2
66°F - 79°F	Zone 2 (N = 707)	Zone 5 (N = 709)	Zone 8 (N = 688)	Zone 11 (N = 548)	Zone 14 (N = 508)	Zone 17 (N = 553)
Normal	96.1	74.2	26.6	22.8	26.6	14.8
Questionable	3.5	19.5	42.9	44.3	32.7	18.4
Very mild	0.4	6.2	28.6	26.6	28.1	27.8
Mild	---	0.1	1.9	5.8	9.6	20.8
Moderate	---	---	---	0.5	2.8	12.8
Severe	---	---	---	---	0.2	5.4
80°F or higher	Zone 3[b] (N = 209)	Zone 6 (N = 335)	Zone 9 (N = 331)	Zone 12 (N = 350)	Zone 15 (N = 310)	Zone 18 (N = 229)
Normal	52.6	32.2	18.1	18.3	8.4	8.3
Questionable	46.9	44.8	51.1	26.0	29.0	18.8
Very mild	0.5	20.0	26.0	37.7	37.5	25.3
Mild	---	3.0	4.2	15.1	17.4	27.9
Moderate	---	---	0.6	2.9	7.4	12.7
Severe	---	---	---	---	0.3	7.0

[a] N = number of children diagnosed.
[b] Fluoride concentration = 0.2 ppm.

Adapted from Richards et al. (1967).

Because the relationship between fluoride concentrations in drinking water and community fluorosis indices was established many years ago, a demand has arisen for evidence confirming or re-establishing the fluoride/fluorosis relationships. Segreto et al. (1984) investigated the possibility that significant changes in cultural and dietary pattern may have altered fluoride intake patterns from those developed 20 to 40 years ago. They selected 16 Texas communities that obtain their drinking water from local wells and surveyed children (7- to 18-years-old) who were lifetime residents of each community for enamel mottling using Dean's (1942) classification system. The fluoride levels in the drinking water was expressed by the authors in terms of the relationship to optimal for prevention of dental caries. Personal communication with one of the authors (Dr. Edwin M. Collins), however, indicated that the actual fluoride levels ranged from 0.2 to 3.2 mg/L (see Table VI-6). The combined incidence of moderate and severe dental fluorosis observed ranged from minimal at 0.2 mg F/L to 31.6 percent at 3.2 mg F/L. The authors, however, reported only one case of severe fluorosis (at 3.2 mg F/L). The observed variation in the fluorosis incidence of different fluoride drinking water levels (see Table VI-6) could be due to differences in the lifestyle in the different communities, variation in the susceptibilities of the children examined or other factors.

Driscoll et al. (1983) reported the results of a cross-sectional survey of the prevalence of dental fluorosis and dental caries among 807 school children (8- to 16-years-old) in seven Illinois communities. Fluoride concentrations in community drinking water ranged from 1.06 to 4.07 mg F/L. The results of this study are summarized in Table VI-7 and indicate a

Table VI-6 Relationship Between Fluoride Levels in Drinking Water and Incidence of Moderate and Severe Dental Fluorosis in Texas Children (Age 7 to 18 Years)

Fluoride level in drinking water		Number of children examined	Combined incidence of moderate and severe dental fluorosis, %[b]
mg F/L[a]	Relative to optimum		
0.2	0.3	103	0.0
0.3	0.4	126	0.0
0.4	0.3	223	0.0
0.8	1.0	361	0.3
1.1	1.3	211	0.9
1.1	1.4	128	0.0
1.1	1.3	187	1.1
1.6	2.5	301	3.3
1.9	2.7	170	13.5
1.9	2.3	23	13.0
2.0	2.3	109	14.7
2.0	2.7	200	4.0
2.3	2.7	90	6.7
2.3	2.9	67	32.8
2.4	3.1	113	4.4
3.2	4.3	190	31.6[c]

[a] Actual concentrations not reported by authors. Values obtained through Personal communication with coauthor (Dr. E. M. Collins).

[b] All cases were classified as moderate dental fluorosis except as noted by footnote.

[c] One case (0.5 percent) was classified as severe dental fluorosis.

Adapted from Segreto et al. (1984).

Table VI-7 Relationship of Drinking Water Fluoride Levels To Dental Fluorosis and Caries Reduction in Illinois Children

Fluoride level in drinking water, mg/L	Number of children evaluated	Children with moderate and severe dental fluorosis, %	Decrease in caries score from 1.06 mg/L level, %[a]
1.06	336	2.4	--
2.08	143	13.3	37.3[b]
2.84	192	27.6	55.1[b]
3.84	136	30.2	35.7[b]

[a] Measured as mean DMF surface score.
[b] Significantly different ($P<0.05$) from score at 1.06 mg/L, but not from each other.

Adopted from Driscoll et al. (1983).

dose-response increase in the incidence of moderate and severe dental fluorosis with increased fluoride level in the drinking water. The incidence of moderate and severe dental fluorosis ranged from 2.4 percent (of 336 children evaluated) at 1.06 mg F/L to 30.2 percent (of 136 children evaluated) at approximately 3.84 mg F/L. Concurrent with this increase in dental fluorosis, the authors observed a significant ($P<0.05$) decrease in dental caries (as measured by reduction of mean DMF surface score) in children of all fluoride levels above 1.06 mg F/L. Unlike the dental fluorosis results, the dental caries reduction was not observed to exhibit a dose-response relationship above the level of 2.08 mg F/L in the drinking water. There was no statically significant ($P<0.05$) difference in the reduction of dental caries between children exposed to an average 2.08 mg F/L through 3.84 mg F/L.

Wenzel and Thylstrup (1982) have suggested that a clinicohistological classification of dental fluorosis may be more sensitive than that described by Dean (1942).

4. Kidney

It does appear that patients with renal impairment have a lower margin-of-safety to fluoride effects than the average person. Hanhijarvi et al. (1972) measured plasma levels of free ionized fluoride in about 2,000 hospital patients in Finland. In patients with normal creatinine clearance, plasma fluoride from individuals living in non-fluoridated areas was about one-half that of people from fluoridated areas (0.7 uM vs 1.4 uM). The authors also noted a correlation between serum creatinine and serum fluoride in renal patients from both the fluoridated and the non-fluoridated areas. Fluoride increased with increasing concentration of serum creatinine in one patient from the non-fluoridated area (serum fluoride increased from 0.8 uM to 3.4 uM while serum creatinine rose from normal to 1,200 uM). In a patient from the fluoridated area, serum fluoride rose from 1.4 uM to 5.0 uM and the corresponding serum creatinine from normal to 700 uM. In renal patients undergoing dialysis, serum fluoride concentrations as high as 25 uM were recorded. These results are consistent with the work of Berman and Taves (1973) who measured renal clearance of serum fluoride in normal and in uremic patients. Normal fluoride clearance averaged 58 mL/min while uremic subjects had a mean fluoride clearance of 3.1 mL/min.

A correlation between renal failure, polyuria, polydipsia, and clinical and roentgenographic evidence of systemic fluorosis was reported by Juncos and Donadio (1972). They discussed two case reports. In one, an 18-year-old male had a daily consumption of about 2 gallons of water from an artesian well containing 2.6 ppm fluoride. His teeth were mottled, very opaque, and caries-free. The patient's normal daily urine volume was 5 to 6 L and clinical indices of renal function were abnormal: inulin clearance (C_{in}) was 26 mL/min (vs 120 mL/min normal), PAH clearance (C_{pah}) was 118 mL/min (vs 600 mL/min normal). Roentgenograms showed increased density of bones. The patient's intake of fluoride from drinking water was about 0.33 mg/kg/day (based on a body weight of 57.4 kg). Similarly, a 17-year-old female with significantly impaired renal function (C_{in}, 19 mL/min; C_{pah}, 99 mL/min), a history of drinking "large amounts of water" and teeth which were opaque with diffuse brownish mottling was found to have marked reduction in renal size, blunting of the calyces, pyelocaliectasis and ureterectasis. The authors did not know whether chronic excessive fluoride intake caused the renal damage but did believe that the systemic fluorosis was due to impaired renal function.

Oreopoulos et al. (1974) examined the effect of fluoride in the dialysate of patients undergoing chronic renal dialysis. In a double-blind study, 20 patients (11 fluoride-exposed and 9 controls) were investigated for an average period of 20.6 months. Dialysate water was initially deionized and fluoride (1 mg/L) or chloride (control) was added via coded ampules. At the end of the study the only difference detected between the control and exposed groups was a statistically significant ($P<0.05$) increase in osteosclerosis in the fluoride-exposed group. No differences in various biochemical, radiological or other histological parameters were detected.

No injuries to the human kidney from long-term non-occupational exposure to fluoride have been reported. Geever et al. (1958) did not find an unusual incidence of renal pathology or renal disease as a cause of death in a population using water containing 2.5 ppm fluoride. No differences in renal status were evident between the residents of Bartlett (8 ppm fluoride in the water supply) and Cameron (0.4 ppm fluoride), Texas (Leone et al. 1954). Urinary excretion of albumin, sugar, red blood cells and formed elements by the children from Newburgh (1.2 ppm fluoride) did not differ significantly from that of the children from Kingston (essentially no fluoride) (Schlesinger et al. 1956a). Abnormalities in renal function, e.g., decreases in urea clearance and glomerular filtration rate, have been reported in Indian subjects with advanced skeletal fluorosis (Shortt et al. 1937a). Water supplies used by these patients contained up to 10 ppm of fluoride (Shortt et al. 1937b).

5. Growth

A possible depression in height, weight and chest circumference has been reported in Japanese children with mottled enamel, compared to control subjects whose teeth were not mottled (Takamori 1955). Water supplies used by these children contained as much as 3.4 ppm fluoride. However, the absence of adequate information on the nutritional status, hereditary background and general state of health of these children makes it difficult to accept these findings as valid. Such observations have not been made in this country. For example, in the Newburgh-Kingston area in New York State, Schlesinger et al. (1956b) found no significant differences in height or weight between the children using fluoridated water for ten years (Newburgh, 1.2 ppm fluoride) and the control population (Kingston, essentially no fluoride). McClure (1944), in a survey of high school boys and young adults living in areas where the water supplies contained up to 6 ppm fluoride, found height and weight to be unrelated to fluoride exposure.

6. Cardiovascular System

Analysis of the death rates from cardiovascular-renal disease in Newburgh and Kingston demonstrated no significant difference in this respect between the two communities (Schlesinger et al. 1956b). Rogot et al. (1978) also found no effect of fluoride in water on heart death rate trends. Geever et al. (1958) reported a lesser percentage of deaths due to cardiovascular disease in persons who had lived more than 20 years in a community where the water supply contained 2.5 ppm fluoride than in persons living 5 to 20 years in that community, but the difference was not attributed to a protective effect of fluoride. A lower incidence of deaths due to heart disease was shown in 20 towns using fluoridated water, compared to 15 towns where the water was not fluoridated (Taves 1978). Luoma et al. (1973) found an inverse correlation between the percentage prevalence of heart disease in male residents of four Finnish communities where fluoride in the drinking water ranged between 0.05 and 2.57 ppm.

Okushi (1954) and Takamori (1955) described mycardial changes seen in children and adults using water supplies containing 0 to 13 mg F/L. The changes described were shown by X-ray or electrocardiography. Unfortunately, in most instances only ranges of fluoride drinking water concentration are given and specific concentrations cannot be associated with the observed changes. However, from a careful examination of the tabular data presented by Okushi (1954), it appears that the lowest-observed-adverse-effect level (LOAEL) was 2.5 mg F/L. Changes observed at this dose included myocardial damage, sinus tachycardia and prolonged P-R and Q-T intervals. One 12-year-old boy consuming water with 2.5 mg F/L showed no signs of myocardial injury. Morever, there may well have been a number of subjects unaffected at this concentration, in as much as the findings were negative in 14 to 16 subjects using waters containing 1.9 to 4.8 mg F/L, but for whom specific concentrations were not identified. Also, positive effects were seen in one child and two adults for whom specific fluoride drinking water concentrations were not specified. Dr. B. Lawrence Riggs (personal communication) was unable to observe any electrocardiographical effects in patients receiving 30 to 63 mg NaF/day or 13.6 to 29.5 mg F/day. Dr. Riggs confirmed this statement after reexamination of the data.

7. Thyroid

No significant effects on the incidence of abnormal clinical findings related to the thyroid gland were seen in long-term residents of Bartlett, Texas, where the water supply contained 8 ppm fluoride (Leone et al. 1954). Geever (1958) examined thyroids taken at autopsy from 728 persons who had used a water supply containing 2.5 ppm of fluoride for periods of less than 5 to more than 20 years. Prolonged use of this water did not significantly affect the incidence of pathological findings in this gland.

D. Teratogenicity

The study by Rapaport (1959) suggested a dose-related association between the number of cases of mongolism registered in institutions and the concentrations of fluoride in the water. This study has been criticized by the Royal College of Physicians (1976). Among the errors cited in the study, the author based his study on fluoride concentrations in the water of the communities where the mothers gave birth, rather than on fluoride in the areas where the mothers lived during pregnancies. These findings have not been substantiated by other reports (Berry 1958, Needleman et al. 1974).

E. Mutagenicity

No data concerning mutagenic effects of fluoride in humans were found in the available literature (IARC 1982).

F. Carcinogenicity

Yiamouyiannis and Burk (1977) presented an analysis of mortality data which showed an increase in the cancer mortality rate among residents of fluoridated areas. This work has been criticized (Strassburg and Greenland 1979, Oldham and Newell 1977). It was shown that Yiamouyiannis and Burk had failed to consider the age-sex-race structure of the populations they studied. Inclusion of these factors in consideration of the data invalidated the conclusion that fluoridation was responsible for an increase in the cancer mortality rate. In other studies, Hoover et al. (1976) and the Environmental Health Directorate of Canada (1977) found no correlation between fluoridation of water and the cancer mortality rate. In addition, the National Cancer Institute, whose data were used as the basis of the study by Yiamouyiannis and Burk, noted errors, omissions, and statistical distortion and stated that, "results of this analysis fail to support any suspicion of hazard associated with fluoridation" (NCI 1975).

The claims of Yiamouyiannis and Burk have also been re-examined by Taves (1979) and by Kinlen and Doll (1981) and found not to be substantiated by the data. Kinlen and Doll have obtained additional information on the numbers of deaths from cancer in the cities concerned, which permits a proper direct method of standardizing cancer death rates. The results were shown to be identical with the standardized rate determined by the indirect method, and both methods indicated less change in cancer mortality rates in the fluoridated cites than in the nonfluoridated cities during the interval 1950 to 1970.

Cook-Mozaffari et al. (1981) and Cook-Mozaffari and Doll (1981) examined cancer mortality in fluoridated and nonfluoridated areas, as well as trends after fluoridation, and concluded there was no evidence from England, Wales, the U.S., Australia or New Zealand that addition of fluoride to water supplies increased the risk of dying from cancer.

The International Agency for Research on Cancer (IARC 1982) concluded there was no evidence that an increased level of fluoride in the drinking water was associated with increased cancer mortality. Similar conclusions had been reached earlier by Rogot et al. (1978) and by the Governor's Task Force on Fluorides (Office of Science and Technology, State of Michigan 1979).

G. Epidemiological Studies

1. Mortality Studies

The largest study of overall mortality rates in high-fluoride (0.7 to 4.0 mg/L) versus low-fluoride (less than 0.25 mg/L) areas considered 32 paired cities (Hagan et al. 1954). The high-fluoride areas had a slightly higher mortality rate than the low-fluoride areas (1,010.6 per 100,000 population versus 1,005.0 per 100,000, respectively). The authors state that this difference is not statistically significant although they did not cite their criterion for statistical significance.

There have been a number of additional statistical evaluations of death rates for all causes and death rates from specific causes in high-fluoride versus low-fluoride areas. The Illinois Department of Public Health (1952) published data on death rates from heart disease, cancer, nephritis, diabetes and all causes in populations using low-fluoride (0 to 0.4 mg/L) surface waters as compared to populations using well waters with higher fluoride concentrations (0.8 to 2.0 mg/L). It was concluded that "mortality experience in Illinois offers little or no support for claims of adverse effects being produced by limited ingestion of fluorides."

An extensive mortality study in Colorado Springs, Colorado, provided information concerning pathological effects in residents after prolonged use of water containing 2.5 mg/L fluoride (Geever et al. 1958). The study was based on 904 necropsies performed by resident physicians in training under the senior author's direct supervision. Necropsy protocols were classified according to the major cause of death, the contributing causes unrelated to the major cause and the incidental pathological condition. Comparative statistical analyses of the pathologic findings revealed no significant differences that could be related to length of residence in the areas. For example, there were three deaths attributed to bone cancer in 334 long-term residents (more than 20 years) and two bone cancer deaths in 188 short-term residents (less than 5 years).

The Ministry of Health (England) reported on mortality and morbidity in high-fluoride (0.4 to 5.8 mg/L) versus low-fluoride (less than 0.2 mg/L) areas (Heasman and Martin 1962). According to the authors, there was no difference in overall mortality between the two groups (approximately 200,000 in each area). Notable was the fact that stomach cancer was shown to be no more prevalent among heavy tea drinkers than among those whose daily consumption of tea was moderate. (Brewed tea adds about 1 mg/L fluoride to the water in which it is prepared.)

2. Skeletal Effects

Leone et al. (1954) compared the effects of exposure to fluoride in drinking water in a high-fluoride area (Bartlett, Texas; 8 mg/L) and a low-fluoride area (Cameron, Texas; 0.4 mg/L). This study commenced in 1943, before the practice of fluoridating drinking water was introduced. A total of 116 individuals living in Bartlett were given thorough physical examinations. As controls, 121 individuals living in Cameron were also examined. The towns were similar with regard to geography and racial composition with the principal occupation in both towns being agriculture. In 1943, 57.8 percent of the Bartlett participants were 55-years-old or older whereas only 47.2 percent of the Cameron participants were in this age category. In 1953, this age category accounted for 55.2 and 46.9 percent of the 10-year participants in Bartlett and Cameron, respectively. Thus, there were more older persons among the Bartlett participants. The male-female ratio for both groups was approximately 1 to 2 in both 1943 and 1953. At 8 mg F/L, the Bartlett water was about eleven times the currently recognized optimum for preventing dental caries under the prevailing climatic conditions.

Both water supply systems had been in continuous use since the turn of the century and the selected individuals in each community had been in continuous residence for at least 15 years at the time of the survey was begun. In 1953, ten years after the initial examinations, follow-up examinations were administered. Average length of fluoride exposure in 1953 was 37 years in the high fluoride area and 38 years in the control area (Leone et al. 1955). All of the original participants were accounted for in the follow-up study.

The results of these examinations are listed in Tables VI-8 and VI-9. The comprehensiveness of the physical examinations is evident from these tables. However, very few statistically significant differences (P=0.05) were found between the two groups. These were limited to greater incidence rates of cardiovascular abnormalities and for urinary albumin, and lower rates for white blood cell counts, neutrophiles and lymphocytes, in the Cameron residents. The nature of the differences, however, does not necessary establish a conclusive dose-response relationship associated with fluoride exposure. It should also be noted that the incidence of bone fractures was greater in the Bartlett residents (Table VI-8). However, this difference was not statistically significant at the P=0.05 level. The greater number of older persons (as well as accident rates, athletic activity and other non-fluoride related factors) in 1953 among the Bartlett participants may have influenced this incidence rate. Dental fluorosis was evident in all Bartlett

Table VI-8 Incidence of Abnormal Clinical Findings, 1943-1953

Characteristic Studied	Bartlett			Cameron		
	Number at Risk	Number Abnormal	Rate %	Number at Risk	Number Abnormal	Rate %
Arthritic change	80	11	13.8	89	13	14.6
Blood pressure						
Sys. 151 mm/Hg and over	58	18	31.0	81	20	24.7
Dias. 100 mg/Hg and over	73	11	15.1	83	11	13.3
Pulse pressure 75 mm/Hg and over	70	9	12.9	89	16	18.0
Bone changes[a]						
Density[b]	74	7	9.5	81	2	2.5
Coarse trabeculation	74	4	5.4	81	2	2.5
Hypertrophic	74	8	10.8	81	6	7.4
Spurs	74	1	1.4	81	4	4.9
Osteoporosis	74	5	6.8	81	10	12.3
Bone, increased density (new cases)	66	1	1.5	79	-	-
Cataract and/or lens opacity	79	8	10.1	85	12	14.1
Thyroid	74	3	4.1	82	6	7.3
Cardiovascular (except uncomplicated hypertension)(c)	80	10	12.5	92	22	23.9
Hearing (decreased acuity)	72	14	19.4	78	10	12.8
Tumor and/or cysts	80	12	15.0	92	10	10.9
Fractures	80	12	15.0	92	7	7.6
Urinary tract calculi	72	14	19.4	76	12	15.8
Gall Stones	73	0	0.0	80	1	1.2

[a] Bone changes determined by simultaneous reading of identical views of X-rays taken in 1943 and repeated in 1953.
[b] Bartlett: 4 increased density, 3 decreased density. Cameron: 2 increased density.
[c] Significant difference between Bartlett and Cameron at $p=0.05$.

Adapted from Leone et al. (1954).

Table VI-9 Prevalence of Abnormal Laboratory Findings, 1943-1953
(Participants Residing in Study Area for the Ten-Year Period)

Laboratory Determination	Year	Bartlett Number Examined	Bartlett Number Abnormal	Bartlett Rate %	Cameron Number Examined	Cameron Number Abnormal	Cameron Rate %	Significant Difference (P = 0.05)
Hemoglobin	1943	116	34	29.3	121	37	30.6	No
	1953	79	20	25.3	83	26	31.3	No
Hematocrit	1943	-	-	-	-	-	-	-
	1953	79	5	6.3	82	7	8.5	No
Red blood cell count	1943	116	25	21.6	121	24	19.8	No
	1953	80	6	7.5	85	2	2.4	No
White blood cell count	1943	116	17	14.7	121	5	4.1	Yes
	1953	78	11	14.1	82	7	8.5	No
Differential count								
Neutrophiles	1943	71	15	21.1	71	6	8.5	Yes
	1953	78	23	29.5	82	13	15.9	Yes
Lymphocytes	1943	71	2	2.8	71	1	1.4	No
	1953	78	35	44.9	82	36	43.9	No
Eosinophiles	1943	71	0	0.0	71	0	0.0	No
	1953	78	6	7.7	82	14	17.1	No
Sedimentation rate	1943	-	-	-	-	-	-	-
	1953	79	31	39.2	83	22	26.5	No
Blood calcium	1943	-	-	-	-	-	-	-
	1953	79	9	11.4	66	7	10.6	No
Serology (S.T.S.)	1943	71	2	2.8	71	3	4.2	No
	1953	84	2	2.4	95	2	2.1	No
Urine albumin	1943	115	3	2.6	121	10	8.3	Yes
	1953	77	5	6.5	85	12	14.1	No
Urine glucose	1943	115	2	1.7	121	4	3.3	No
	1953	77	0	0.0	85	1	1.2	No

Adapted from Leone et al. (1954).

participants who were born and in continuous residence there during the formation of the permanent dentition. There was also one instance of dental fluorosis in a Cameron resident with a history of early fluoride exposure.

Leone et al. (1955) reported a comparison of radiographs taken in 1943 and 1953 of the participants in the Bartlett-Cameron study. The findings reported were limited to an evaluation of anterior-posterior views of the lumbar spine, sacrum, pelvis, trochanters and the proximal one third of the femur. These regions were chosen because the earliest and most definitive skeletal changes associated with fluoride occur in these areas. In 1943, 16 of the Bartlett residents showed "roentgenographic bone changes in varying degree . . . considered of interest to this study." Ten years later, nine of these subjects showed no further bone changes, four showed increased bone density, three showed a decrease toward a "normal" appearance and one new case of increased bone density was identified.

The radiographs indicated that in persons using the water supply containing 8 mg/L fluoride about 10 to 15 percent of the population who resided in the Bartlett area for an average of 37 years experienced an increased bone density (with or without coarsened trabeculation) with a "ground-glass" appearance. Other observations included coarsened trabeculation, showing lines of stress without increased bone density and increased thickening of cortical bone and periosteum with equivocal narrowing of the bone marrow spaces. These changes are slight, often difficult to recognize and in most instances equivocal in nature. Apparently, these changes are not deleterious within the level of statistical significance for this study because there was no unusual incidence of bone fracture, arthritis, hypertrophic bone changes or exostoses; no interference with fracture healing; no cases of "poker back"; and no evidence of associated functional or systemic effects. Bone biopsy samples for the determination of fluoride concentrations were not taken.

The study by Leone et al. (1954) is the only one of its kind available on U.S. residents who have used high-fluoride waters for a prolonged period. It is interesting to note that only a small proportion of the study population in Bartlett was affected to the extent described by Leone et al. (1954). It should be noted that Singh and Jolly (1970) called attention to the fact that advanced radiological changes reported from hyperendemic areas of India are not universally seen in the population as a whole. Singh and Jolly (1970) have suggested that nutritional status, other sources of fluoride intake and involvement in heavy labor in a hot climate may influence the incidence of severe fluorosis in these Indian populations. We have no information on these factors in the Texas communities studied by Leone et al. (1954). However, the possibility of hard work in hot temperatures, resulting in the ingestion of large amounts of water, may be a significant factor for these two agricultural communities.

Leone et al. (1960) compared the radiological findings from 546 residents between 30- and 70-years-old of Framingham, Massachusetts, (0.04 mg/L fluoride) with those of residents of Bartlett, Texas, (8.0 mg/L fluoride) and Cameron, Texas, (0.4 mg/L fluoride) cited earlier by Leone et al. (1954). The prevalence of increased bone density and coarsened trabeculation were significantly less in Framingham than in Bartlett, and comparable to the rates observed in Cameron. The prevalence of ligamentous calcification (bone spurs) was higher in Framingham. Also, there was an unusually high number of cases of osteoporosis in the Framingham population. The authors suggest that deleterious effects on the bone structure of adults may be associated with prolonged use of low-fluoride waters.

Stevenson and Watson (1957) reported roentgenographic changes typical of fluorosis. In this study, medical records on file at the Scott and White Clinic (Temple, Arizona) for the period from 1943 through 1953 were examined. Only 23 instances of a roentgenographic diagnosis of fluoride osteosclerosis were found in a total of approximately 170,000 roentgen examinations of the spine and pelvis. These cases were associated with individuals (44- to 85-years-old) who resided in Texas or Oklahoma and, in one instance, in Kansas. Four of the 23 subjects used water containing 8.0 mg F/L, three used water containing 7.6 mg F/L, seven used water containing 5.0 to 5.4 mg F/L and one used water containing 4.0 mg F/L. Specific water supplies and fluoride concentrations were not identified for the remaining eight persons, however, they all lived in areas known to be high in fluorides. The earliest changes were observed in the pelvis and lumbar spine and consisted of slightly increased bone density and a slight "ground-glass" appearance. The most advanced changes encountered were a chalky white appearance of the vertebral column and pelvis, and a slightly increased density and coarse trabecular pattern in the ribs. There was slight roughening of the periosteum of bones of the forearm or legs in a few patients. Calcification of the sacrospinous and sacrotuberous ligaments was also observed. No relationship was evident between the roentgenographic findings and the clinical diagnosis of the patients' condition. Stevenson and Watson (1957) concluded that roetgenographically detectable fluoride osteosclerosis was not produced by drinking water containing less than 4 mg F/L.

Hodges et al. (1941) concluded that prolonged use of water supplies up to 3 mg F/L did not cause radiologically demonstrable sclerosis of the skeleton. In this study roentgenograms were made of the pelvis and lower lumbar spine of 86 subjects who had used water supplies containing 1.2 to 3.0 mg F/L for none to 61 years (ages were 7.5 to 71 years), and of 31 subjects 18- to 78-years-old who had used drinking water containing approximately 2.5 mg F/L for 18 to 68 years. Generalized skeletal sclerosis was not observed in any of these 117 subjects.

Dinman et al. (1976) evaluated 56 persons occupationally exposed to airborne fluorides in the aluminum industry. In this study preshift urinary fluoride concentrations less than 4 mg F/L were apparently not associated with increased bone density, alteration of trabecular patterns or ligamentous calcification, as revealed by X-ray examination. According to Figure III-3 a urinary concentration of 4 mg F/L in adults corresponds to a concentration of approximately 4 mg F/L in the drinking water.

3. Effects in Children

One of the earliest fluoridation studies involved complete pediatric examinations during the first ten years of exposure to elevated fluoride levels. Five hundred children in Newburgh, New York, "the fluoridated city" (1.2 mg/L fluoride in the drinking water), were compared to 405 children in Kingston, New York, the control city ("essentially fluoride-free"). The examinations included roentgenograms (of the right hand and wrist, both knees and the lumbar spine), blood and urine analyses and general physical examinations. Smaller groups of children were subjected to special tests including; visual acuity, hearing levels and additional urine analyses. The urine analyses were designed to evaluate if fluoride had an irritating effect on the kidneys. After evaluation of the data from all examinations, it was concluded that there were no differences of medical significance between the two groups of children (Schlesinger et al. 1956b, Ast et al. 1956). Specifically, with regard to bone, there was no evidence of increased bone density or alteration in rate of skeletal maturation.

McCauley and McClure (1954) compared radiographs of the right hand and wrist for a total of 2,050 children, 7- to 14-years-old, residing in Amarillo or Lubbock, Texas, to those in Cumberland, Maryland. The drinking water in the communities contained 3.5 to 4.4, 3.3 to 6.3 and 0.1 mg/L fluoride, respectively. Skeletal age and quantitative index of ossification were derived from the radiographs. The data indicated that calcification of the carpal bones of the children was not affected by exposure to fluoride, nor was there any evidence of advanced skeletal maturity and bone development. In as much as development of bones of the hand and wrist parallels that of the rest of the skeleton, the authors concluded that skeletal development throughout the body was not affected by fluoride exposure.

Skeletal fluorsis in children has not been reported in this country. However, skeletal effects have been described in Indian children and children in Tanzania. Teotia et al. (1971) found diagnostic radiological findings in six Indian children, 11- to 14-years-old. Water from four wells in the district of Rai Bareli Uttar Pradesh contained 10.35 to 13.5 mg/L fluoride. The duration of symptoms was one to ten years. Grossly limited movements of the spine, thoracic kyphosis and flexion deformities of the hips and knees (suggesting crippling fluorosis) were present in four children. Mottled discoloration of the teeth was present in five cases. Skeletal radiographs showed osteosclerosis of the spine and pelvis in six cases. Four cases demonstrated coarsened trabeculation in the knees and elbows and calcification of the interosseous membrane of the forearm.

Teotia et al. (1979) examined 550 children, 4- to 15-years-old, from the same district of India and found diagnostic radiological findings in 200 of the children. The effects observed included; osteosclerosis (particularly of the spine, pelvis and thorax), periosteal bone formation, exostoses and calcification of ligaments, interosseous membrane and muscle attachments. Roentgenological findings typical of hyperparathyroidism were seen in 43 cases. Of the 200 children with diagnostic radiological changes, 32.5 percent were symptom-free, 67.5 percent were symptomatic, 51.5 percent were without crippling deformities and 16.5 percent were crippled. All of the children showed mottled discoloration of the teeth. Water from four wells in the area contained 24 to 26 mg/L fluoride.

Wenzel et al. (1982b) examined the effects of fluoride on dental enamel, skeletal maturity and bone structure in 11- to 15-year-old Tanzanian girls. The children were born and raised in areas where the drinking water contained < 0.2, 1.5, 2.5 or 3.6 mg/L fluoride. Dental fluorosis was positively associated with fluoride concentration in the drinking water. No conclusions could be drawn regarding the effect of fluoride in the water on skeletal maturity. This was attributed to differences among the groups in nutritional state and exposure to disease. There was, however, a correlation between retardation of skeletal maturity with increasing dental fluorosis for the group using water containing 3.6 mg/L fluoride. The authors suggest that increased fluoride exposure slows skeletal maturation. However, due to the very warm climate of Tanzania, drinking water intake would have a significant impact on the total dose. Such a relationship was not evident in a similar study of 12- to 14-year-old Danish girls whose drinking water contained < 0.2 or 2.4 mg/L fluoride (Wenzel et al. 1982a).

4. Other Studies

Other epidemiological studies include one in Russia (Knizhnikov 1958) where the health of natives of Shchuchinsk (3.4 to 4.0 mg F/L) was compared with that of natives in Kokchetav (0 to 0.9 mg F/L). In addition to the usual examinations of bones and teeth, the participants were examined for hypertension, bradycardia, somnolence, coagulation of blood, parathesis and urticaria-type rash. All of the illnesses listed were less frequent in the fluoride area than in the control area with the exception that severe dental fluorosis was prevalent in the fluoride area. Also, there was an unexplained and unusually low incidence of diseases of bones, muscles and joints in the fluoride area.

A case-control study in South Carolina concluded that high fluoride concentrations in drinking water (4.18 mg F/L) exert a protective effect against the development of primary degenerative dementia (Still and Kelley 1980). The authors hypothesize that fluoride attenuates the neurotoxicity of aluminum. There are some weaknesses in the study, one of which is that it was based on hospital admissions rather than on occurrence rates.

H. Summary

Fluoride has been shown to have several beneficial effects, both in terms of general health and in the treatment of specific diseases. Numerous studies have documented the benefits provided by fluoride in preventing dental caries in children. Many of these studies evaluated the transition to adverse dental effects (fluorosis) at higher dose levels. Conclusions from these studies indicate that the beneficial effects are obtained and the adverse effects prevented when the drinking water (in an average temperature climate) is approximately 1 mg/L.

Fluoride has been demonstrated to have a positive effect on bone development and has found application in stimulating new bone growth in patients with osteoporosis. To a lesser degree, fluoride has also been suggested to have possible effects on the cardiovascular system (i.e., reduced aortic calcification when drinking water contained 4.0 to 5.8 mg F/L) and hearing (i.e., stabilization of the sensorineural component of hearing loss in patients with active otospongiosis when 40 to 60 mg was administered daily).

A "certainly lethal (single) dose" of NaF for a 70-kg man is estimated to be 5 to 10 g or 70 to 140 mg/kg. Fluoride may cause a wide variety of toxic effects in humans. Among these, the claims of allergic or idiosyncratic sensitivity, mongolism and cancer have not been substantiated. On the contrary, sound evidence suggests that fluoride does not cause sensitivity, mongolism or cancer. There is evidence which suggests that persons with chronic renal insufficiency may have a lower margin-of-safety for the toxic effects of fluoride.

Chronic exposure to either too low or too high a concentration of fluoride may have deleterious effects on the skeletal system. An increase in the incidence of severe osteoporosis was correlated with use of drinking water containing 0.4 mg/L fluoride. Severe skeletal fluorosis has been reported in persons living in areas of naturally high fluoride concentrations (up to 14 mg/L). Radiologically detectable osteosclerosis has been observed in about 10 percent of long-term residents using water supplies containing 8 mg/L fluoride. Retardation of skeletal maturity has been observed in children using a water supply containing 3.6 mg/L fluoride. In other situations, skeletal fluorosis has not been described in populations whose water supplies contained less than 4 mg/L fluoride.

An important effect of fluoride is dental fluorosis (mottled enamel). Numerous studies have examined the relationship between concentrations of fluoride in community drinking water supplies and the occurrence of dental fluorosis. Some studies have determined that the acceptable level of fluoride in water varies with the mean annual temperature of the area in question, because people drink more water when the environment is warmer. In one study, concentrations of fluoride causing cosmetically "objectionable" dental fluorosis varied from 0.8 mg/L at mean temperature of 70°F to 1.7 mg/L at mean temperature of 50°F (estimated to equal 0.05 mg/kg/day). The Agency, however, has concluded that there is insufficient data to quantitatively incorporate temperature in any future drinking water regulations. Concentrations associated with intentional fluoridation of drinking water (0.7 to 1.2 mg/L) have not shown adverse effects on health or longevity. Factors considered include growth, effects on the kidney, cardiovascular system and thyroid, teratogenicity and mutagenicity.

VII. ADDENDUM TO CHAPTER VI. HEALTH EFFECTS IN HUMANS

Since the publication of the Draft Drinking Water Criteria Document on Fluoride (USEPA 1985a), the Environmental Protection Agency (USEPA) has received and reviewed a number of scientific papers on the health effects of fluoride in humans. The major observations of this review (USEPA 1985b) are summarized below:

1) Two cases of crippling skeletal fluorosis have been observed in the U.S. associated with the consumption of drinking water (Goldman et al. 1971; Sauerbrunn et al. 1965). Crippling skeletal fluorosis was noted in both a 55 year old male (Goldman et al. 1971) and a 64 year old male (Sauerbrunn et al. 1965), who drank large but unknown quantities of drinking water over a period of 20 or more years. The amount of water consumed is estimated to be 6 L per day containing, respectively, somewhere between 2.4 and 3.5 mg fluoride/L in one case and between 4.0 and 7.8 mg/L in the other. In addition, both individuals consumed large quantities of tea daily (amount unspecified) which also contributed to their fluoride intake.

2) Additional information has become available that fluoride is not oncogenic: The Report of the Working Party on the Fluoridation of Water and Cancer - i.e. Knox Report (Knox 1985). The Working Party was charged by the Government of Great Britain "to reappraise the published and otherwise available data and conclusions on cancer incidence and

mortality amongst populations whose drinking water is either artificially fluoridated or contains high levels of fluoride from natural sources". The Knox Report concluded: "We have found nothing in any of the major classes of epidemiological evidence which could lead us to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, is capable of inducing cancer, or of increasing the mortality from cancer. This statement applies both to cancer as a whole, and to cancer at a large number of specific sites. In this we concur with the great majority of scientific investigators and commentators in this field. The only contrary conclusions are in our view attributable to errors in data, errors in analytical techniques, and errors in scientific logic".

3) Additional information has become available that fluoride does not have any adverse effects upon the teeth. Eklund et al. (1984) concluded that the consumption of drinking water containing 4 mg/L or less does not result in any adverse effect upon the teeth (e.g. periodontal disease) and that the consumption of drinking water containing 4 mg/L, as compared to 0.7 mg/L, results in an increase in the level of dental attrition (wearing away of the teeth) "which does not appear to be of any clinical importance".

4) Other than crippling skeletal fluorosis which is extremely rare in the U.S., no data was found which requires a major change in the conclusions reached in the Criteria Document.

VIII. MECHANISMS OF TOXICITY

A. Acute Effects

The mechanism by which fluoride causes acute lethality at high doses has not been fully defined. Obviously, there is interference with the normal metabolism of cells and essential enzymatic reactions may be blocked. There may be interference with the origin and transmission of nerve impulses, perhaps as the result of calcium complex formation. Other metabolic roles of calcium may be interrupted (e.g., blood clotting and membrane permeability). Also, there may be severe renal tubular damage and injury to the mucosa of the stomach and intestine. Vomiting and diarrhea result in appreciable water loss, electrolyte imbalance and a clinical picture of shock (Hodge and Smith 1965).

B. Skeletal Effects

Fluoride is involved in bone mineral deposition in several ways. It may be essential to the precipitation or nucleation of the apatite lattice in an orderly fashion on collagen fibers. Fluoride from extracellular fluid exchanges with hydroxyl ions and perhaps bicarbonate ions in the surface layer of hydroxyapatite crystals to form fluorohydroxyapatite. This material shows an increased crystalline structure and less solubility than does hydroxyapatite. Fluoride is incorporated into the inner layers of the crystal lattice, as well as on the surface of newly formed crystals, by the accretion of new mineral. Osteoclastic resorption of old bone and osteoblastic deposition of new bone, resulting in continual remodeling of the skeleton, allows release and re-uptake of fluoride into bone mineral. Fluoride apparently increases the rate of formation of new bone, the number of osteoblasts and the serum activity of the osteoblastic iso-enzyme skeletal alkaline phosphatase. The effects of fluoride may be modulated by parathyroid hormone and by human skeletal growth factors (Neuman et al. 1950, McCann and Bullock 1957, Smith et al. 1953, Zipkin et al. 1958, Hodge and Smith 1981, Faccini and Teotia 1974, Farley et al. 1983).

C. Dental Effects

Evidence suggests that dental fluorosis results from effects of fluoride on the ameloblasts. Developing enamel and enamel-forming cells are the first to respond when rats are injected with sodium fluoride. The newly formed enamel matrix is faulty and poorly mineralized. The staining frequently seen with mottled teeth may be the result of oxidation of organic material integrated in the dental structures. It has also been suggested that it may be related to food pigments which have penetrated the hypoplastic enamel. Mottling, however, does not determine the degree of dental fluorosis (Schour and Smith 1934, Schour and Poncher 1937, Shupe et al. 1963, Gabovich and Ovrutsky 1969, Dean 1934).

D. Summary

The mechanism for acute lethality at high fluoride dose levels is not fully defined. It is believed that certain essential enzymatic reactions may be blocked and there may be interference with the origin and transmission of nerve impulses. The metabolic roles of calcium and physical damage to the kidney and the mucosa of the stomach and intestine are also believed to be associated with the acute lethality mechanism. Fluoride interacts with bones and teeth by replacing hydroxyl or bicarbonate ions in hydroxyapatite to form fluorohydroxyapatite. Fluoride may function as an essential key to bring about precipitation or nucleation of the apatite lattice in an oriented fashion on collagen fibers. Accretion of new mineral continues, and fluoride, brought to the surfaces of newly formed crystals by the extracellular fluid, replaces the hydroxyl ion. As crystal growth continues, fluoride is incorporated into inner layers of the crystals as well as on the surface. Remodeling of the bone structure takes place by an interplay of osteoclastic resorption of old bone and osteoblastic deposition of new bone. The presence of fluorohydroxyapatite increases the crystalline structure of the bone and reduces its solubility. Available evidence suggests that dental fluorosis results from toxic effects of fluoride on the epithelial enamel organ. Specifically, several investigators have shown that ameloblasts are susceptible to fluoride. Dental staining often accompanies fluorosis but does not itself determine the degree of fluorosis. The staining is believed to be due to the oxidation of organic material in defective enamel or the penetration of hypoplastic sections of enamel by food pigments.

IX. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. An Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day)(Body Weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.

- An uncertainty factor of 1,000 is used when limited or incomplete acute or chronic toxicity data in all species are available or when the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species, but human data are not available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify fluoride as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

It has been concluded, however, that the foregoing risk assessment procedures are not appropriate for application with the available fluoride data. The typical assessment assumes a high to low dose extrapolation will be made. In the present case, the extensive availability of human data requires an interpolation rather than extrapolation. Possibly more important is that the typical assessment procedure does not provide for any quantitative inputs for a chemical's potential beneficial effects. Fluoride has well documented beneficial effects that must be addressed (balanced) during the assessment. Thus, the assessment that will be performed for fluoride must rely largely upon an interpolation of the available human data and give due consideration to balance the required degree of human health protection from adverse effects with the documented beneficial effects.

A. Non-Carcinogenic Effects

1. Short-Term Exposure

Acute toxic effects in the human following ingestion of fluoride have been described by Lidbeck et al. (1943). In this instance, ingestion resulted from the inadvertent mixing of roach powder containing sodium fluoride with food being served in an institution, but no reliable measure of the amount of fluoride ingested was possible. The initial effect of rapidly ingesting large amounts of fluoride is irritation of the gastrointestinal tract, causing vomiting and diarrhea. Both the vomitus and the feces may contain blood. These symptoms may proceed to collapse and eventual death (Lidbeck et al. 1943). No single target system appears uniquely susceptible to these acute effects, suggesting that fluoride acts as a general systemic poison at very high doses. This explanation is consistent with the ability of high concentrations of fluoride to bring about a state of shock, to inhibit essential enzymatic processes such as cellular respiration and to interfere with essential roles of calcium (Hodge and Smith 1965).

Black et al. (1949) described the effects of fluoride administered to more than 70 patients for periods of five to six months. Most of these subjects, suffering from malignant neoplastic disease, were being treated with metabolic inhibitors. Some were leukemic children 3 to 6.5 years old, while others were adults including elderly individuals. Doses for the children were 20 to 50 mg NaF (9.0 to 22.5 mg F) four times daily. Doses for adults were 80 mg NaF (36.3 mg F) four times daily. The material was administered orally with an antacid containing 4 percent aluminum oxide or as an enteric coated tablet to avoid gastric irritation. No evidence of systemic toxicity or of parenchymatous damage was seen which could be attributed to fluoride, even though some patients had received more than 27 g of sodium fluoride over a period of three months. Criteria evaluated included growth and development in the children, mottled enamel, eruption of permanent teeth, hematopoiesis, liver function, albumin-globulin ratio, blood sugar and cholesterol concentrations and kidney function. Postmortem data from four cases showed no parenchymatous degeneration attributable to fluoride. In hypertensive patients a tendency was noted for decreased diastolic and systolic blood pressure. In two patients with functioning colostomies there was no apparent effect of fluoride on the exposed mucosa of the colon.

2. Long-Term Exposure

Comprehensive investigations by Shupe et al. (1963) evaluated the effects of fluoride on dairy cattle to include changes observed in the teeth. In this study pairs of cows were fed rations containing 12 (normal), 27, 49 or 93 ppm fluoroxide on a total dry matter basis. Feeding was continued from 4 months to 7.5 years of age. Depending upon the amount of fluoride ingested, affected teeth erupted with different degrees of mottling, staining, hypoplasia and hypocalcification. The following tooth classifications were established:

(0) Normal: smooth, translucent, glossy white enamel; tooth normal shovel shape.

(1) Questionable effect: slight change, exact cause not determined; may have enamel flecks; cavities may be unilateral or bilateral but with the absence of mottling.

(2) Slight effect: slight mottling of enamel; may have slight staining but no wear; teeth normal shovel shape.

(3) moderate effect: definite mottling and staining of enamel; coarse mottling (large patches of chalky enamel); teeth may have slight signs of wear.

(4) Marked effect: definite mottling, staining and hypoplasia; may have pitting of enamel; definite wear of teeth; enamel may be a pale cream color.

(5) Excessive effect: definite erosion of enamel with excessive wear of teeth; staining and pitting of enamel may or may not be present.

In cattle consuming the highest dose of fluoride (i.e., 93 ppm in the ration) the incisors were classified as 4 to 5, beginning as early as two years of age. The molars were classified as 0 to 3 at two years of age, 1 to 4 at four years and 1 to 5 at six years. For cattle at the dose of 49 ppm, the incisors were scored as 3 to 4 beginning at two years. In these same animals, the molars were scored as 0 to 1 at two years, 1 to 2 at four years, and 1 to 3 at six years. In cattle administered 27 ppm fluoride, the incisors were scored as 0 to 2 through six years of age and the molars were scored as 0 to 1 through six years. Incisors and molars of cattle administered the normal ration (12 ppm fluoride) were scored 0 to 1 throughout the six years.

Richards et al. (1967) indicate that objectionable dental fluorosis (moderate and severe according to the classification scheme by Dean 1942) in humans appears with the following combinations of waterborne fluoride concentrations and mean annual temperatures:

- 1.4 to 1.6 ppm fluoride at 65°F or less.
- 1.1 to 1.3 ppm fluoride at 65°F to 79°F.
- 0.8 to 1.0 ppm fluoride at 80°F or higher.

These values are similar to those reported by Galagan and Lamson (1953) as shown in Figure VI-1 (see Section VI). In the classical scheme for rating fluorosis, teeth diagnosed as normal exhibit no clinically observable evidence of exposure to fluoride. Richards et al. (1967) suggest that such teeth should be classified as fluoride deficient rather than normal. Their data indicate that as the percentage of children showing clinical evidence of mild fluorosis approaches four to six percent, some objectionable (moderate) fluorosis begins to appear.

Because the relationship between fluoride concentrations in drinking water and community fluorosis indices was established many years ago, a demand has arisen for evidence confirming or re-establishing the fluoride/fluorosis relationships. Segreto et al. (1984) investigated the possibility that significant changes in cultural and dietary patterns may have altered fluoride intake patterns from those developed 20 to 40 years-ago. They selected 16 Texas communities and surveyed children (7 to 18 years old) for enamel mottling using Dean's (1942) classification system. The fluoride levels in the drinking water were expressed by the authors in terms of the relationship to optimal for prevention of dental caries. Personal communication with one of the authors (Dr. Edwin M. Collins), however, indicated that the actual fluoride levels ranged from 0.2 mg/L to 3.2 mg/L. The combined incidence of moderate and severe dental fluorosis observed ranged from minimal at 0.2 mg F/L to 31.6 percent at 3.2 mg F/L. The authors, however, reported only one case of severe fluorosis (at 3.2 mg F/L). The observed variation in the fluorosis incidence at different fluoride drinking water levels could be due to differences in the lifestyles of the different communities, variation in the susceptibilities of the children examined or other factors.

Driscoll et al. (1983) reported the results of a cross-sectional survey of the prevalence of dental fluorosis and dental caries among 807 school children (8 to 16 years old) in seven Illinois communities. Fluoride concentrations in the community drinking water ranged from 1.06 to 4.07 mg F/L. The results of this study indicate a dose-response increase in the incidence of moderate and severe dental fluorosis with increased fluoride level in the drinking water. The incidence of moderate and severe dental fluorosis ranged from 2.4 percent (of 336 children evaluated) at 1.06 mg F/L to 30.2 percent (of 136 children evaluated) at approximately 3.84 mg F/L. Concurrent with this increase in dental fluorosis, the authors observed a significant ($P<0.05$) decrease in dental caries (as measured by reduction of mean DMF surface score) in children of all fluoride levels above 1.06 mg F/L. Unlike the dental fluorosis results, the dental caries reduction did not exhibit a dose-response relationship above the level of 2.08 mg F/L in the drinking water. There was no statistically significant ($P<0.05$) difference in the reduction of dental caries among children exposed to an average 2.08 mg F/L through 3.84 mg F/L.

A summary of the incidence of moderate and severe dental fluorosis from six studies spanning more than 40 years (1937 to 1984) is provided in Table IX-1. The data assembled in this table are from six different sources, each with technically sound but varied procedures, analytical methods

Table IX-1 Summary of Moderate and Severe Dental Fluorosis in Children

Fluoride drinking water concentration (mg/L)	Number of children evaluated	Dental fluorosis incidence,%		Reference[a]
		Moderate	Severe	
0.2	103	0.0	0.0	6
0.3	126	0.0	0.0	6
0.4	223	0.0	0.0	6
0.4	82	0.0	0.0	4
0.4	263	0.0	0.0	4
0.5	113	0.0	0.0	4
0.5	403	0.0	0.0	4
0.6	614	0.0	0.0	4
0.7	316	2.0	0.0	4
0.8	95	2.0	1.0	4
0.8	361	0.3	0.0	6
0.9	123	0.0	0.0	4
1.0	50	0.0	0.0	4
1.1	336	1.8	0.6	3
1.1	211	0.9	0.0	6
1.1	187	1.1	0.0	6
1.1	128	0.0	0.0	6
1.2	70	13.0	3.0	4
1.2	633	0.0	0.0	4
1.2	152	0.0	0.0	4
1.2	171	0.0	0.0	4
1.3	447	0.0	0.0	4
1.5	110	0.9	0.0	2
1.6	301	3.3	0.0	6
1.8	57	3.5	0.0	2
1.8	170	1.2	0.0	1
1.9	273	1.1	0.0	1
1.9	170	13.5	0.0	6

continued-

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[a] References:
1 = Dean (1942) as summarized by Albertini et al. (1982).
2 = Dean and Elvove (1937) as summarized by Albertini et al. (1982).
3 = Driscoll et al. (1983).
4 = Galagan and Lamson (1953) as summarized by Albertini et al. (1982).
5 = Lewis and Faine as summarized by Albertini et al. (1982).
6 = Segreto et al. (1984).

Table IX-1 - continued

Fluoride drinking water concentration (mg/L)	Number of children evaluated	Dental fluorosis incidence,%		Reference[a]
		Moderate	Severe	
1.9	23	13.0	0.0	6
2.0	109	14.7	0.0	6
2.0	200	4.0	0.0	6
2.1	143	8.4	4.9	3
2.2	179	13.4	0.0	2
2.2	138	11.0	0.7	1
2.3	90	6.7	0.0	6
2.3	67	32.8	0.0	6
2.4	113	4.4	0.0	6
2.5	148	14.2	3.4	2
2.6	404	8.9	1.5	1
2.9	192	7.8	8.3	3
2.9	97	23.7	3.1	2
3.2	190	31.1	0.5	6
3.8	21	9.0	0.0	5
3.9	136	7.4	22.8	3
3.9	289	33.9	13.2	2
4.0	39	38.0	6.0	5
4.0	101	40.0	2.0	5
4.0	59	23.7	11.9	2
4.2	39	33.0	3.0	5
4.4	189	46.0	17.9	2
4.8	36	6.0	0.0	5
5.7	38	50.0	39.5	2
7.6	65	10.8	58.5	1
8.0	21	47.6	42.9	2
14.1	26	38.5	53.8	1

and sample sizes. Therefore, no effort has been made to merge these findings into a single dose-response distribution or to perform any statistical analysis of the assembled data. The table is provided to supply a consolidated sampling of the historical data on dental fluorosis incidence and to conveniently reflect the general dose-response relationship of increased dental fluorosis with increased dose. It should be noted, however, that the incidence of objectionable dental fluorosis (moderate and severe) does not generally impact a significant percentage of the population until the drinking water concentration approaches 2.0 mg F/L.

At the request of the EPA, the U.S. Surgeon General examined the relationship of fluoride in drinking water and the aspects of dental fluorosis. The results of that evaluation (Koop 1982, Albertini et al. 1982) led to the general conclusion that, while not considered an adverse health effect, the undesirable cosmetic effects to teeth could be minimized by limiting the fluoride concentration to twice the optimum for the reduction of dental caries. The Surgeon General encouraged communities to limit water to twice optimum (about 2 mg F/L) to provide this protection for children up to age nine, but emphasized that there is no sound evidence to indicate that adverse effects on general or dental health (dental fluorosis was not judged to be an adverse effect) are associated with concentrations of fluoride that are naturally found in U.S. public water supplies. The Surgeon General repeated his earlier opinion on limiting fluoride concentrations to twice the optimum (about 2 mg F/L) in his response to a subsequent EPA request to evaluate the nondental effects of fluoride (Shapiro 1983, Koop 1984).

The EPA, with the assistance of the National Institute of Mental Health (NIMH), convened an ad hoc Review Panel of behavioral scientists to investigate the potential psychological and/or behavioral effects associated with dental fluorosis. This ad hoc Review Panel reviewed background information and conducted a meeting on October 31, 1984 in Bethesda, MD to discuss this issue and determine if consensus opinions could be formulated. The conclusions and recommendations of the Review Panel's deliberations were summarized in a November 17, 1984 report (Kleck 1984) and are repeated below:

> "It is concluded that individuals who have suffered impaired dental appearance as the result of moderate to severe (dental) fluorosis are probably at increased risk for psychological and behavioral problems or difficulties. Since this conclusion is based on extrapolations from research on the effects of physical appearance characteristics other than dental fluorosis, it is suggested that investigations be supported to directly assess the social, emotional, and behavioral effects of fluoride-induced cosmetic defects. Finally, the Panel recommends research be done on the further development of techniques for the amelioration or removal of the unaesthetic appearance effects associated with some levels of dental fluorosis."

Skeletal changes in bones of cattle ingesting 12 (normal), 27, 49 or 93 ppm fluoride on a total dry matter basis have been described by Shupe et al. (1963). Fluoride concentrations in dry, fat-free rib biopsy samples increased with increasing time of exposure for all dose groups. After 7.3 years (2,663 days) the fluoride concentration was approximately 900 ppm in animals on the normal diet. At this same time, the rib fluoride concentrations were approximately 2,500, 5,500 and 8,200 for the cattle receiving 27, 49 and 93 ppm fluoride in the ration, respectively. The rate of increase with time was greatest in those cattle administered 93 ppm fluoride.

The first clinically discernible bone lesions appeared on the medial surface of the proximal third of the metatarsal bones and were bilateral. These effects were observed after 1.5 to two years in cattle on the 93 ppm fluoride ration and after 3.5 to four years in cattle on the 49 ppm fluoride ration. As the degree of osteofluorosis increased, palpable hyperostoses appeared in the rami of the mandibular bones, and the 7th through 12th ribs became wider and thicker. The degrees of periosteal hyperostosis were classified as 0 = normal, 1 = questionable, 2 = slight, 3 = moderate, 4 = marked and 5 = excessive. Cattle on the normal diet were scored as normal through six years of age. Those cattle on 27 ppm ration were scored 0 to 1 through six years; those on 49 ppm ration were scored 0 to 2 at two years, 0 to 3 at four years, and 0 to 4 at six years; and those on 93 ppm ration were scored 0 to 3, 0 to 4 and 0 to 5 at two, four and six years, respectively. Radiographs taken at age 7.5 years (approximately seven years on fluoride) showed increased coarsening and thickening of the trabecular pattern with a ground glass appearance for cattle on the rations containing 49 and 93 ppm fluoride. Periosteal hyperostosis, subperiosteal increased density in some cases, endosteal and cortical porosity and mineralized spurs at points of attachment of tendons to leg bones were also observed at these dose levels.

Leone et al. (1955) described roentgenographically detectable changes observed in 10 to 15 percent of persons residing an average of 37 years in Bartlett, Texas where the water supply contained 8 mg F/L. Observations included increased bone density with or without coarsened trabeculation, with a "ground glass" appearance; coarsened trabeculation, showing lines of stress, without increased bone density; and increased thickening of cortical bone and periosteum with equivocal narrowing of bone marrow spaces. Bone biopsy samples for the determination of fluoride concentrations were not taken.

Stevenson and Watson (1957) reported an increase in bone density and a definite but slight "ground glass" appearance in spinal and pelvic roentgenograms of 23 subjects who were long-term residents of high fluoride areas in Texas, Oklahoma and Kansas. For 15 of these individuals, the drinking water contained 4 to 8 mg F/L. The fluoride content of the drinking water was unknown for the remaining eight subjects. Calcification of the sacrospinus and sacrotuberous ligaments was also evident in 15 of the 23 subjects. Although a total of 170,000 X-ray films were examined, the authors were unable to develop a meaningful incidence rate because information was lacking as to the total number of films examined for persons exposed to specific levels of fluoride.

Hodges et al. (1941) examined roentgenograms of the pelvis and lumbar spine of 86 persons (7.5 to 71 years old) who had used water supplies containing approximately 1.2 to 3 mg F/L for up to 61 years. They found no occurrence of generalized sclerosis. A second population (ranging in age from 18 to 78 years) which had used a water supply containing approximately 2.5 mg F/L for 18 to 68 years was similarly evaluated. Again, no instance of generalized skeletal fluorosis was observed.

Wenzel et al. (1982b) observed a significant relationship of dental fluorosis and reduced skeletal maturity in 11- to 15-year-old Tanzanian girls whose drinking water contained only 3.6 mg/L of fluoride. The authors suggested that increased fluoride exposure slows skeletal maturation. Due to the warm climate (i.e., increased exposure and total dose), dietary and other factors, the relevance of these results to the U.S. population is not well established.

There is limited evidence to permit an estimate of the waterborne fluoride concentration associated with the appearance of fluoride osteosclerosis. For example, Hodge and Smith (1970) quote evidence that in the aluminum industry, average urinary excretions of 5 mg F/L in randomly collected samples are not associated with osteosclerosis. Dinman et al. (1976) indicated that aluminum workers whose average pre-shift urinary fluoride concentration is less than 4 mg F/L do not show radiographically demonstrable increases in bone density, altered trabecular patterns or ligamentous calcification. According to Figure III-3 (see Section III for greater detail), urinary fluoride concentration is essentially equal to the concentration of fluoride in the drinking water ingested at steady-state exposure conditions. Thus, the absence of clinically or radiographically demonstrated osteosclerosis in the studies cited by Hodge and Smith (1970) and by Dinman et al. (1976) could be estimated to be associated with exposures to drinking water containing approximately 5 and 4 mg F/L, respectively. Smith and Hodge (1959) have suggested that, in the human, osteosclerosis probably will not be seen with skeletal fluoride concentrations of 4000 ppm (dry fat-free basis). They also state that effects will be observed in a small proportion of individuals with skeletal fluoride concentrations of approximately 6,000 ppm. These skeletal concentrations correspond to fluoride concentrations in the water of 4 and 6 mg F/L, respectively (Smith and Hodge 1959, Hodge and Smith 1981).

At the request of the U.S. Environmental Protection Agency (EPA), the U.S. Public Health Service (PHS) conducted an evaluation of the nondental health effects of fluoride. At the direction of the Surgeon General an ad hoc committee was assembled to review the available literature. The committee met on April 18-19, 1983 in Bethesda, MD and summarized their findings in a report to the Surgeon General (Shapiro 1983). That report was formally transmitted to the EPA with a letter from the Surgeon General on January 23, 1984.

The committee listed the nondental health effects of fluoride as: (1) death (acute poisoning); (2) gastrointestinal hemorrhage; (3) gastrointestinal irritation; (4) arthralgias; and (5) crippling fluorosis. Gastrointestinal effects are not known to occur at fluoride concentrations in drinking water. In adults, mild osteosclerosis, as opposed to crippling fluorosis, is not considered an adverse effect.

Based on their review of the available literature the Surgeon General's ad hoc committee made the following conclusions (Shapiro 1983):

1. It is inadvisable for the fluoride content of drinking water to be greater than twice the current optimal level (1.4 to 2.4 mg/L) for children up to age 9 in order to avoid the uncosmetic effects of dental fluorosis. This conclusion coincides with the recommendations of the Surgeon General relative to the dental effects of naturally occurring fluorides.

2. The fluoride content of drinking water should not be greater than four times the optimal level for any community water supply. This conclusion recognizes that, fluoride intake from water between 5.0 and 8.0 mg/L (4 times to 10 times optimum) has been associated, in a very small number of subjects, with the radiologic appearance of early osteosclerosis, which while not an adverse health effect, is however, an indicator of demonstrable osseous changes not to be anticipated at lower levels (less than four times optimum) of fluoride.

3. The difference between 4 times and 10 times optimum represents an adequate margin-of-safety unless further research warrants reconsideration of these levels. There exists no directly applicable scientific documentation of adverse medical effects at levels of fluoride below 8 mg/L (ppm). Therefore, it can be concluded that four times optimum in U.S. drinking water supplies is a level that would provide "no known or anticipated adverse effect with a margin-of-safety."

4. The effects of various levels of fluoride intake on rapidly developing bone in young children are not well understood. Also, the modifying effects of total intake, length of exposure, other nutritional factors and debilitating illness are not well understood. Therefore, the committee strongly recommends that the PHS and the EPA join to enlarge the body of information relative to skeletal maturation and growth in children ingesting more than the recommended daily intake of fluoride.

B. Quantification of Non-Carcinogenic Effects

As stated earlier, the extensive amount of health effects information on humans and the need to establish a balance between adverse and beneficial effects prevents use of the typical risk assessment approach to derive appropriate drinking water concentration values for fluoride. Thus, the approach selected must rely largely upon an interpolation and direct application of the available human data on adverse and beneficial effects.

1. One-Day and Ten-Day Health Advisory

There is an absence of appropriate short-term animal or human experimental or clinical studies on the effects of fluoride following oral ingestion from which one-day or ten-day Health Advisory (HA) values can be calculated. The National Academy of Sciences Safe Drinking Water Committee has reviewed the available literature on fluoride, but did not recommend a suggested-no-adverse-response-level (SNARL) for fluoride (NAS 1977).

2. Adjusted Acceptable Daily Intake

Dental Fluorosis. As stated earlier, the available date on the incidence of dental fluorosis in humans (especially children) is extensive. As summarized in Table IX-1, the incidence of objectionable (moderate and severe) dental fluorosis is not consistently observed in a marked segment of the population until the drinking water concentration approaches 2.0 mg F/L. This observation is consistent with the Surgeon General's recommendation (arthralgias) are not likely to occur at human dose levels below 20 mg F/day (10 mg F/L for an adult consuming 2 L water/day). The ad hoc committee concluded that four times the optimal fluoride concentration (approximately 4 mg F/L) in drinking water should provide an adequate margin of safety for preventing adverse health effects which were not documented to occur in the U.S. population below 8 mg F/L.

Singh and Jolly authored a review of the skeletal effects of the fluoride (WHO 1970). Their conclusion stated:

> "It is, therefore, possible to conclude that the histopathological changes of endemic fluorosis occur only at higher levels of intake than 1-4 ppm."

In a more recent survey of fluoride by WHO (1984), it was stated that "...at 3.0 to 6.0 mg/L skeletal fluorosis may be observed; when 10 mg/L is exceeded, crippling fluorosis could ensue." It should be noted that both WHO summaries consider the effects of fluoride on worldwide populations. Thus, their conclusions may not be directly applicable to the U.S. situation.

Both the Surgeon General's and WHO's evaluations of the available health effects data on skeletal fluorosis appear to be generally consistent with the primary published literature. The investigations with human subjects by Leone et al. (1955), Stevenson and Watson (1957), Hodges et al. (1941), Hodge and Smith (1970) and Dinman et al. (1976) provide evidence that the no-observed-adverse-effect-level (NOAEL) for the initial symptoms of skeletal fluorosis (arthralgias) are not likely to occur at human dose levels below 20 mg F/day (10 mg F/L for an adult consuming 2 L water/day). The ad hoc committee concluded that four times the optimal fluoride concentration (approximately 4 mg F/L) in drinking water should provide an adequate margin of safety for preventing adverse health effects which were not documented to occur in the U.S. population below 8 mg F/L.

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C. Carcinogenic Effects

No valid studies on the carcinogenic potential of fluoride in animals were located in the literature. However, the National Cancer Institute initiated studies during August 1979 to determine the carcinogenic and or toxicological potential of sodium fluoride (NaF) in rats and mice. The National Toxicology Program (NTP) took over the responsibility for oversight of the studies in November 1982. The studies consisted of three parts: (1) a one-month subchronic study; (2) a six-month subchronic study with dosages based on the previous experiment; and (3) a two-year chronic study based on data from the six-month subchronic experiment (maximum doses of NaF which were not expected to affect the longevity of mice and rats were used). The chronic study began in December, 1981 and terminated in December, 1983. Unfortunately, problems developed seven months into the chronic study. The problems were not treatment related (some rats in both the treatment and control groups exhibited toxicollis and ocular lesions) but may have been related to the diet which was low in several trace elements and vitamins. The validity of the study was questioned and a new chronic study was scheduled. The Technical Report from the new study should be issued in 1988.

Yiamouyiannis and Burk (1977) presented an analysis of mortality data which they claimed showed an increase in the cancer mortality rate among residents of fluoridated areas. Later analyses (Strassburg and Greenland 1979, Oldham and Newell 1977) have shown that Yiamouyiannis and Burk had failed to consider the age-race-sex structure of the studied populations. Inclusion of these factors in consideration of the data invalidated the conclusion that fluoridation was responsible for an increase in the cancer mortality rate. Other studies by Hoover et al. (1976) and the Environmental Health Directorate of Canada (1977) found no correlation between fluoridation of water and the cancer mortality rate. Further, the International Agency for Research on Cancer (IARC) has performed an assessment of the degree of evidence for the carcinogenicity of fluoride in humans and in experimental animals (WHO 1982). This assessment concluded that no evidence could be found in the literature to indicate that fluoride is carcinogenic.

D. Existing Guidelines and Standards

Protection for the industrial worker against excessive exposure to airborne fluoride is achieved by occupational standards set by OSHA and based on the American Conference of Government Industrial Hygienists Threshold Limit Value (TLV) for airborne fluoride of 2.5 mg/m^3. This is a concentration which should not cause an adverse health effect in a person so exposed for eight hours/day, five days/week (NAS 1971). The Pennsylvania Short-Term Limit for exposure to airborne fluoride is 10 mg/m^3 for 30 minutes. This concentration is permissible as long as the TLV is observed on a time-weighted basis (NAS 1971).

Under the requirements of the National Interim Primary Drinking Water Regulations of 1975 (USEPA 1976), EPA set the standards (MCL) for fluoride shown in Table IX-2. These levels are twice the concentrations defined as optimal for the control of dental caries. The EPA (USEPA 1979) defined "unreasonable risk to health" as a fluoride concentration producing moderate to severe fluorosis, or specifically, a Community Fluorosis Index exceeding 1.5. In theory, the Index of 1.5 would correspond to fluoride concentrations exceeding the established MCL for fluoride (twice the optimum for each temperature zone).

The Food and Nutrition Board of the National Research Council has estimated adequate and safe total intakes of fluoride as shown in Table IX-3. These levels are considered to be protective against dental caries and possibly against osteoporosis (NAS 1980).

Table IX-2 Maximum Contaminant Levels[a]

Temperature		Concentration
Degrees Fahrenheit	Degrees Celsius	Milligrams per liter (ppm)
53.7 and below	12.0 and below	2.4
53.8 to 58.3	12.1 to 14.6	2.2
58.4 to 63.8	14.7 to 17.6	2.0
63.9 to 70.6	17.7 to 21.4	1.8
70.7 to 79.2	21.5 to 26.2	1.6
79.3 to 90.5	26.3 to 32.5	1.4

[a] Highest permissible concentration of a contaminant in the water delivered to the consumer's tap.

Adapted from USEPA (1976).

Table IX-3 Food and Nutrition Board Estimated Adequate and Safe Intakes of Fluoride

Age group	Estimated weight (kg)	Recommended intake of fluoride (mg/day)	Estimated equivalences(mg/kg/day)
<6 months	6	0.1-0.5	0.02-0.08
6-12 months	9	0.2-1.0	0.02-0.11
1-3 years	13	0.5-1.0	0.04-0.08
4-6 years	20	1.0-2.5	0.05-0.13
7 years-adulthood	30[a]	1.5-2.5	0.05-0.08
Adults	70	1.5-4.0	0.02-0.06

[a] Estimated weight for children seven to ten years old.

Adapted from NAS (1980).

The Association for the Advancement of Medical Instrumentation has suggested a maximum concentration of 0.2 mg F/L for water being used in dialysis. The specific health effects basis for selection of this value, however, is not stated (Association for the Advancement of Medical Instrumentation 1981).

The Canadian Public Health Association (1979) recommended that 1.2 mg F/L be established as the optimum concentration in that country's drinking water.

The World Health Organization (WHO 1970), after an extensive review of the health effects of fluoride, concluded that: "When nutrition is adequate, enrichment of water so that it contains 1.0 to 1.2 ppm is advisable in temperate zones. In warmer regions, the content should be smaller." The derivation of these suggested levels for fluoride is not specifically explained. The suggestion is made after an extensive review of the literature on the relationship of fluoride levels to dental caries experience and to dental fluorosis. In the preface to this publication (WHO 1970) it is stated that "The objective of this monograph is to provide an impartial review of the scientific literature...It is not intended to be a practical guide to the use of fluoride as a health measure...."

More recently the World Health Organization (WHO 1984) stated that, "at (drinking water) levels above 1.5 mg/L, mottling of teeth has been reported very occasionally, and at 3.0 to 6.0 mg/L skeletal fluorosis may be observed...." This review is based largely upon information in the 1970 WHO Monograph (WHO 1970) and further states that no new evidence has been obtained to justify modification of the current 1.5 mg/L guideline value for fluoride in drinking water. The report cautions that "local climatic conditions and increased water intake should be considered when applying this recommended guideline value." The WHO reference to occasional skeletal fluorosis with the consumption of drinking water in the range of 3.0 to 6.0 mg F/L is an estimate of the lower limit for this effect under a variety of environmental and nutritional conditions that are not necessarily reflective of the U.S. situation.

The NAS (1977) has discussed fluoride in their document on drinking water and health. This work includes several comments pertinent to the estimation of an MCL for fluoride:

> On the basis of studies done over 15 years ago, occasional objectionable mottling would be expected to occur in communities in the hotter regions of the United States with water that contains fluoride at 1 ppm or higher and in any community with water that contains fluoride at 2 ppm or higher. However, this may not be the case today; more liberal provisional limits seem appropriate while studies are conducted to clarify the subject.
>
> ...it was estimated that objectionable fluorosis occurs in the range of 0.8-1.6 mg/liter fluoride, depending on the temperature. No recent U.S. surveys or studies of communities have been found on which a sound decision could be made that greater concentrations are without objectionable effect.
>
> ...there is no generally accepted evidence that anyone has been harmed by drinking water with fluoride concentrations considered optimal for the annual mean temperature in the temperate zones.

In Gabovich and Ovrutsky (1969), a translated Russian review document, it is stated that "All Union State Standard 2784-54" (USSR) has set by law the fluorine concentration of 1.5 mg/L as the maximum permissible amount in tap water. After discussing the effect of ambient temperature on fluorosis, they say that (p. 612), "In year-round fluoridation of the water with a single dose of fluorine, the Commission on Hygiene of the Water Supply and Sanitary Protection of Bodies of Water at the Ministry of Health of the USSR recommends 1 mg/L for regions with cold and temperate climates, for warm climates 0.9 mg/L, and 0.7 to 0.8 mg/L for hot climates." Gabovich (1952, cited in Gabovich and Ovrutsky 1969) made the following comments concerning various concentrations of fluoride in drinking water:

- Up to 0.3 mg/L is a very low concentration. At this concentration the incidence of caries is high and defects in the mineralization of bones are most frequently observed.

- Water with 0.7 to 1.0 mg/L has an optimum concentration. Damage by caries is minimal, signs of dental fluorosis are also minimal.

- Fluoride concentration is high at 1.0 to 1.5 mg/L, but acceptable with permission of the health authorities. Caries control is good and there are signs of mild fluorosis. This level is acceptable in the absence of data indicating an unfavorable influence on the health of the population.

- Concentrations of 1.5 to 2.0 mg/L are higher than the permissible level. Caries control is good, but fluorosis is objectionable.

- Two to six mg/L is a high concentration. Caries control is not optimal and fluorosis is objectionable with 10% to 30% having severe fluorosis.

- Six to fifteen mg/L is a very high concentration. Caries control is not optimal and up to 100% of the population are afflicted with fluorosis, with the predominance of the severe forms.

Gabovich and Ovrutsky (1969) state that the Indian standard for fluoride in water is 1 mg/L (permissible) with 2 mg/L not permissible.

E. Special Considerations

1. High Risk Populations

Relatively small segments of the general population may be at increased risk from waterborne fluoride. For example, polydipsia and polyuria associated with diabetes insipidus and some forms of renal impairment may result in an excessive intake of drinking water and waterborne fluoride. Skeletal fluorosis in patients with impaired renal function has been described by Juncos and Donadio (1972). Patients with impaired renal function have been shown to have a lesser renal clearance of fluoride than have normal subjects (Schiffl and Binswanger 1980).

2. Beneficial Effects

a. Teeth

The principal beneficial effect attributed to fluoride is its role in prevention of dental caries. A detailed review of the literature in this area will not be attempted here because it has been adequately addressed elsewhere in this document. Studies have been reviewed that describe the continuum from beneficial effects to dental fluorosis with increased exposure to fluoride. A summary of the daily fluoride intake levels considered to be protection against both dental caries and possibly osteoporosis is provided in Table IX-3.

Fluoride is also believed to improve the esthetic appearance of teeth. A. L. Russell recorded the occurrence of developmental enamel hypoplasias (not related to fluoride in drinking water) in children 7 to 14 years old (Ast et al. 1956). In Kingston, where the drinking water contained 0.05 mg F/L, 115 (18.7 percent) of the 612 children examined showed these nonfluoride opacities. Only 36 (8.2 percent) of 438 children using the fluoridated Newburgh water (1.0 to 1.2 mg F/L) showed these changes. Ast et al. (1956) suggested that this fluoride drinking water concentration (1.0 to 1.2 mg F/L) appeared to reduce the incidence of hypoplastic spots on the teeth.

b. Bone

Jowsey et al. (1972) described the effects in 11 patients with progressive osteoporosis who were administered 30, 45, 60 or 90 mg of NaF daily. The patients, ten of whom were female, ranged from 54 to 72 years of age. All subjects received vitamin D twice weekly and a daily supplement of calcium. Treatment was continued for 12 to 17 months. The results indicated that administration of less than 45 mg of NaF daily did not consistently increase bone formation, but that 60 mg or more resulted in the production of abnormal bone. Side effects were evident in at least one patient receiving 30 mg NaF. Mild arthralgia and stiffness of the joints were reported by four patients and occasional epigastric dyspepsia was experienced by six patients. Daily addition of vitamin D and more than 600 mg Ca appeared to prevent increased bone resorption and even to decrease resorption. The authors concluded that doses of 50 mg of NaF daily, supplemented with 600 mg or more of calcium daily and 50,000 units of vitamin D twice weekly should increase skeletal mass without undesirable skeletal effects. Also, further vertebral fractures should cease after several years of treatment.

Dambacher et al. (1978) treated 33 post-menopausal women with 100 mg NaF daily for two years and another 23 similar patients with 50 mg NaF daily for two years. A decrease of cortical bone was evident at both dose levels. However, cancellous bone was increased to some extent in half of those receiving the lower dose, and in over 70 percent of those receiving the higher dose. The findings also suggested that two years of treatment at the lower dose or one year at the higher dose avoided new vertebral fractures. Gastrointestinal discomfort sometimes combined with nausea was encountered chiefly at the higher dose, but was of minor clinical importance. Osteoarticular pain was the major side effect of fluoride therapy and was seen in about 60 percent of the patients at both dose levels. The maximum effect was seen after 6 to 12 months of treatment and then gradually disappeared. In 18 percent of the patients treatment had to be discontinued.

Riggs et al. (1982) studied five groups of women, totaling 165 patients, during the period from 1968 to 1980. Fluoride was given (1) with calcium with or without vitamin D and (2) with calcium and estrogen with or without vitamin D. Doses were 40 to 60 mg NaF daily with a total of 61 patients (of 165 total) receiving fluoride. Of these, 23 (38 percent) developed adverse reactions which caused five of them to withdraw from the study. These effects were not seen in the control patients or in the other experimental groups (those treated with calcium alone or with vitamin D, or with calcium plus estrogen with or without vitamin D).

Among the patients treated with NaF, 60 percent showed radiographically demonstrable increases in vertebral bone mass. Patients with these changes showed about one-seventh the fracture rate of the other patients. The incidence of fractures per 1000 patient-years for patients treated with fluoride, calcium and estrogen (with or without vitamin D) was significantly less than in controls ($P<1 \times 10^{-6}$) and also was significantly less than in those treated with fluoride and calcium (with or without vitamin D) ($P<0.001$). The authors believe vitamin D should not be included because of the increased incidence of hypercalcemia or hypercalciuria or both.

Berstein et al. (1966) compared the incidence of osteoporosis, reduced bone density and collapsed vertebrae in two populations using water supplies with different concentrations of fluoride. In this study, a roentgenogram of the lateral lumbar area of the spine and answers to a questionnaire were obtained for 166 males and for 134 females who were long-term residents of areas where the water supplies contained 4 to 5.8 mg F/L. Similar information was obtained for 312 male and 403 female long-term users of water supplies containing 0.15 to 0.3 mg F/L. More than 50 percent of the participants in each area had never lived outside their respective areas. The subjects of each sex in each population were grouped by age into those 45 to 54 years old, 55 to 64 years old and 65 years old and over. Evidence of osteoporosis, reduced bone density and incidence of collapsed vertebrae were higher in the low fluoride area in both sexes. For women 55 to 64 years old and 65 years old and older the difference in prevalence of reduced bone density was significant at the $P<0.01$ level. In men the difference was significant only for the 55- to 64-year-old group ($P<0.05$). More subjects in the high fluoride area had normal or increased bone density. There was no significant difference in the incidence of collapsed vertebrae among male residents of the two areas. For women, the greater incidence of collapsed vertebrae in the low fluoride area was significant at the $P<0.05$ and $P<0.01$ levels for the 55- to 64-year-old and the 65-year-old and over groups, respectively. The authors concluded that 4 to 5.8 mg F/L in drinking water "materially and significantly" reduced the prevalence of osteoporosis and collapsed vertebrae, and that the effects were more pronounced in women than in men.

c. Cardiovascular

In the study by Bernstein et al. (1966) the incidence of aortic calcification (as seen in the X-ray films) was less in residents of the high fluoride area than in those using low fluoride water. The difference was approximately 40 percent and was statistically significant for men in all age groups. Women in the 55- to 64-year-old group also showed a statistically significant difference in the incidence of calcification. A similar trend, although not statistically significant, was observed in females 65 years of age and older.

d. Hearing

Shambaugh and Causse (1974) treated more than 4,000 patients with active otospongiosis of the cochlear capsule with sodium fluoride for 1 to 8 years, using doses of 40 to 60 mg daily with calcium and vitamin D supplements. The fluoride was administered in enteric coated tablets. In about 80 percent of the treated patients there was a stabilization of the sensorineural component of hearing loss, with recalcification and inactivation of the actively expanding demineralized focus of otospongiosis. In a few cases hearing was improved, while in others the hearing loss continued to worsen. In a number of instances, cessation of therapy after stabilization of hearing and recalcification had been achieved was followed (two to seven years later) by reappearance of a demineralized focus and an increase in the sensorineural loss. Shambaugh and Causse (1974) recommended a maintenance dose of 20 mg daily of sodium fluoride after stabilization has been achieved.

Causse et al. (1980) gathered more evidence for the beneficial effect of fluoride therapy on otospongiotic foci through polytomographic studies, statistical analysis of 10,441 cases (with a follow-up of three months to ten years) and by comparing trypsin concentration in the perilymph before and after NaF therapy. Trypsin, which is toxic to hair cells and destroys collagen fibrils in the bony otic capsule, was significantly (no P value given) reduced in 66% of cases at moderate NaF (45 mg/day) doses. Fluoride therapy causes expulsion of cytotoxic enzymes into labyrinthine fluids and retardation of sensorineural deterioration. The long-term effect of therapy is the reduction of the bone remodelling activity of the otospongiotic focus. NaF therapy (in patients with cochlear deterioration and progressive cochlear component) can improve hearing in children but can only arrest deterioration in older patients. NaF may retard, but cannot release, stapedial fixation. Fluoride action reduces vertigo as an effect on vestibular function. Dosages used by the authors range from 3 to 60 mg/day depending on the nature of the otospongiotic impairment (in children only 1.5 to 10 mg/day are prescribed to avoid stunting growth). The authors observed no fluorosis in more than 10,000 cases.

3. Interactions

Aluminum salts inhibit the absorption of fluoride, as has been shown by Hobbs et al. (1954). Incorporation of aluminum sulfate into the ration of livestock resulted in an increase of fecal excretion of fluoride, a decrease in urinary excretion, decreased skeletal storage and lessened mottling of incisor teeth.

4. Relative Source Contribution

Approximately one million persons in the U.S. use water supplies which contain more than twice the local optimal concentration for prevention of dental caries. These people live in about 1,200 communities, mostly in the southwest (Small 1983). Water supplies used by some of these communities may contain more than 4 mg F/L. In general, waterborne fluoride concentrations are higher west of the Mississippi River than they are in the eastern part of the continental U.S. (Smith 1983a). Further, the highest concentrations in water supplies are observed in areas where the soil is rich in apatite or other fluoride minerals and the water is obtained from wells (NAS 1971). Frequently these higher fluoride areas are in regions where the annual mean temperatures are somewhat elevated. As a result, water consumption may be higher and the fluoride intake by the population increased.

According to the National Institute for Occupational Safety and Health (NIOSH 1976) there were approximately 22,000 workers exposed to hydrogen fluoride in 57 different occupations and 350,000 workers exposed to inorganic fluorides in 92 occupations. These workers are exposed to airborne fluorides during their working hours, but the concentrations are limited by Occupational Safety and Health Administration standards intended to prevent the development of skeletal fluorosis. There is no evidence that individuals occupationally exposed to fluorides and using fluoridated water have developed radiographically demonstrable skeletal fluorosis.

F. Summary

While there is considerable variation in the numerous epidemiological studies performed, it is believed that the incidence of objectionable (moderate and severe) dental fluorosis begins to impact a marked segment of the population when the drinking water concentration approaches 2.0 mg F/L.

The available human data indicate that the no-effect-level for the initial symptoms of skeletal fluorosis (increased bone density) is between 3.0 to 8.0 mg F/L. The NOAEL for crippling skeletal fluorosis in the U.S. is believed to be at drinking water concentrations at or above 10.0 mg F/L. Thus, a drinking water concentration of 4.0 mg F/L is considered to provide adequate protection for crippling skeletal fluorosis with a margin of safety.

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